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TITLE: "Transitioning the Defense Automated Neurobehavioral Assessment (DANA) to Operational Use."

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14. ABSTRACT

This grant prepares DANA (Defense Automated Neurobehavioral Assessment), the next-generation neurocognitive assessment tool (NCAT), for transition into operational military use. The effort is organized around two foci – **science** and **transition**. The science concentrates on CONUS-based studies such as testing DANA in clinical drug, fatigue/alertness, concussion and/or depression protocols. All studies have completed data collection. Data analysis and manuscript preparation are currently underway. Ongoing analysis shows promise regarding DANA's applicability. The second thrust, transition, included obtaining FDA clearance for DANA and positioning DANA to be operationally deployed into the military.

15. SUBJECT TERMS
Neurocognitive Assessment Tool, DANA, cognition, concussion, depression, PTSD, transition, database, FDA clearance, normative data

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Table of Contents

INTRODUCTION:
This 24-month effort assisted in the preparation and transition of DANA (Defense Automated Neurobehavioral Assessment), the next-generation neurocognitive assessment tool (NCAT), into operational military use, as well as prepared DANA for use in CONUS clinics. DANA is a clinical decision support tool developed for and funded by the Department of Defense (DOD) for use in field and clinical settings. The effort was organized around two foci – **science** and **transition**. The second thrust, transition, included obtaining FDA clearance for DANA (DOD has determined it is a medical device), and positioning DANA to be operationally deployed into the military.

KEYWORDS: Neurocognitive Assessment Tool, DANA, cognition, concussion, depression, PTSD, transition, database, FDA clearance, normative data

ACCOMPLISHMENTS:
What were the major goals of the project?
Science Objectives
Task 1: IRB approval for data collection for three studies
Task 2: Subject Identification for the three studies
Task 3: Data Collection for three studies
Task 4: Data Analysis for three studies
Task 5: Reporting for three studies

Transition Objectives
Task 6: Obtaining FDA Clearance
Task 7: DANA Reliability and Validity Publications

What was accomplished under these goals?

Key Research Accomplishments

- Submission of a 510(k) application to the FDA and obtaining clearance for DANA.
- Development of a relational database to store our datasets, as well as created an automated way of cleaning our datasets to prepare them for data analysis.
- Obtainment of normative data collection on a military population in order use this data as a standard reference measure among military populations.
- JHU (depression study): preliminary data analysis shows that DANA provides more sensitivity than the MMSE in a clinical population diagnosed with major depressive disorder. Results of this study are forthcoming as data analysis is currently underway. ***(Preliminary analysis in Appendices O and P)***
- The VA study (PTSD study) showed that DANA could be used to track cognition over time in a home based telehealth model. ***(Preliminary analysis in Appendix Q)***
- UW (concussion study): preliminary findings show that the DANA Spatial sub-test may be sensitive to concussion. ***(Preliminary analysis in Appendix N)***
- Numerous manuscripts have been published showing that DANA a reliable, consistent assessment tool.
- DANA is being evaluated by an Integrated Product Team (IPT) as a step in the acquisition process.

Task 1: IRB approval for data collection

Once the revised SOW for this effort was approved, we moved forward in obtaining IRB

approval for each study proposed. In each of our studies, we partnered with another organization, and as the data was collected at that partner's facility, and under their administration, each host was required to submit the specific protocol for that study to his/her respective IRB. Once the study-specific IRB had approved the protocol, it was submitted to MRMC for Army IRB approval. To date, all three studies obtained approval and are in the data analysis stages.

Task 2: Subject Identification for the three studies

Following guidance from the Scientific Advisory Panel members and as indicated in the revised Statement of Work (approved 6/18/13), we identified classes of subjects for the following studies proposed:

1 Concussion Study (IRB Protocol #: PRO 16061)

We collaborated with Dr. Michael McCrea (Medical College of Wisconsin) and Dr. Alison Brooks (University of Wisconsin). The purpose of this study was to compare the assessment of cognitive function immediately after concussion and during recovery from moderate-severe TBI using DANA and ImPACT. 250 student athletes in football and soccer were to be baselined using both devices, and then 33 concussed and 33 matched controls were to be assessed for concussion in a direct head to head comparison over the season. Measurements included pre-injury baseline assessment, acute (<24 hours post) evaluation, and follow-up assessments 8, 15 and 45 days post-injury. To date, 250 athletes have been baselined, as well as 20 concussed and 20 matched controls.

2 Depression Study (Application #: NA_00082172)

DANA Rapid was used to assess cognitive functioning in patients with major depressive disorder undergoing Electroconvulsive Therapy. We believe DANA could provide a more sensitive assessment of cognitive function following therapy than current assessment tools. Baseline measures were recorded prior to therapy, then again at three intervals after therapy. An N of 20 ECT, and 20 controls was anticipated. Drs. Adam Kaplin, Steven Woods and Kristen Rahn, Departments of Psychiatry and Neurology, Johns Hopkins University School of Medicine, led the study. 17 subjects were baselined in the ECT treatment group and 16 in the non-ECT group, and data collection has been completed.

3 PTSD Study (Project #: 2013-03/JLS/PROMISE0007)

The primary purpose of the PTSD study conducted by our partners, Pacific Health Research and Education Institute (PHREI), was to provide psychological data and to analyze the longitudinal data in support of the transition of DANA to operational use. Using DANA, clinicians and research assistants collected longitudinal data from Service Members and civilians for analysis by Dr. Spira and his team. The aggregate data will be used to establish and confirm referential norms and recovery patterns. ATinc is responsible for data organization, additional analysis, and reporting. 48 subjects have been baselined, all in the experimental treatment group, and data collection has been completed.

4 Additional studies considered

We considered conducting a fatigue study at WRAIR as well as a daily "ALERTNESS" study at NICoE, but the length of time needed to obtain the necessary IRB approval threatened to render an unacceptable constraint in terms of data collection and analysis. We are proceeding with seeking approval, and depending on when, and if, obtained will use IRAD dollars to proceed with this study. As of the final report, WRAIR has not received IRB approval for this effort.

While we were unable to launch a fatigue study directly with WRAIR, WRAIR has pursued separate studies with DANA. WRAIR presented a poster at MHSRS 2015 on DANA that examined the relationship between neurocognitive and driving performance during 50 hours of sleep deprivation in subjects receiving caffeine or placebo. Performance over time was assessed and the relationships between performance metrics were sought in an effort to predict operational performance using DANA. ***(Appendix I)***

Task 3: Data Collection

Data collection has been completed for the three studies described below. For the concussion study, we partnered with the University of Wisconsin and have baselines for 82 football athletes. For the PTSD study, we partnered with the VA and have baselines for 73 subjects. On the Depression study with JHU, we have 17 patients consented for the ECT group and 16 for the control group.

Normative Data Collection:

A healthy population of active-duty military, aged 18-64, provide a relevant range of subjects by which a normative database, representative of the larger population of active-duty members can be used for the purpose of neurocognitive test comparison when baseline information is not provided or cannot be easily obtained.

In order to determine how many subjects per age bin were required for comparison we ran power analysis calculations ***(Appendix V).*** It was determined based off of these calculations that 50 subjects per age bin was the minimum number required to yield significant data. ***(Appendix V)***.

Normative data was collected under the direction of Dr. Michael Russell at Ft. Hood. We obtained normative data for 824 subjects (240 female, and 584 male). We have stored and coded the norms in our database by age bins ranging from 18-64 years old as well as gender.

Task 4: Data Analysis

Significant preparations were made with respect to performed analyses. These include:

- Meeting several times with data analysts to receive statistical advice on different ways to approach longitudinal correlations and data analysis.
- Conducting analysis of current cross-sectional and longitudinal DANA data to determine sensitivity and specificity for power estimates of DANA studies to be conducted as part of the RIF protocols.
- Consulting with various statisticians to reach consensus on how to handle anomalous data, e.g., lapses, anticipatory responses, outliers.

- Extensive discussions with statisticians to determine the optimal sample size of treatment and control groups. With some of the more complex study designs, we made a deliberate attempt to optimize subject size so as to minimize unnecessary costs and arrive at the most efficient design.
- Reviewing and selecting RIF longitudinal protocols.
- Reviewing past DANA pilot studies to accurately ascertain inter class reliability (ICC) and reliable change indexes (RCI).
- Developed a relational database to house all study data and created an automated cleaning system in order to streamline our ability to quickly begin data analysis.

Study Outcomes:

1. UW Concussion Study (IRB Protocol #: PRO 16061)

Baseline Testing Overview:

- Baseline testing started on 2/26/14 and completed 3/3/14 for spring 2014 football– 82 athletes.
- Baseline testing started on 6/4/2014 and completed by 9/22/14 for 2014-2015 season for football, soccer, basketball, ice hockey – 228 athletes.
- August 2014 – 7 injured athletes started post-injury testing.
- September 2014 – 2 injured athletes started post-injury testing; 7 controls started testing; 4 injured athletes completed day 45 testing.
- October 2014 – 3 injured athletes started post-injury testing; 5 controls started testing; 3 injured athletes completed day 45 testing; 5 controls completed day 45 testing.
- November 2014 – 2 injured athletes started post-injury testing; 1 control started testing; 4 injured athletes completed day 45 testing; 4 controls completed day 45 testing.
- December 2014 – 2 injured athletes
- January 2015 – 2 injured athletes
- March 2015 – 7 injured athletes
- April 2015 – 3 injured athletes
- As of June 8, 2015, all data collection and entry is complete with: 232 DANA baselines. There were 28 concussed athletes – (14 football, 4 women's soccer, 4 men's soccer, 2 men's basketball, 3 women's hockey and 1 men's hockey). All 28 concussed athletes and controls completed post-injury testing.
- Data Analysis, Interpretation, Reporting and Dissemination are now currently in progress. Manuscript preparation will be on going as data is analyzed.
- Internal preliminary data analysis was completed comparing healthy controls with concussed ***(Report is in Appendix N).***

2. JHU Depression Study (Application #: NA_00082172)

- Completed study recruitment; final study numbers are N=16 for controls, and N=17 for ECT patients. Data analysis is now underway.
- Presented oral presentation at a Public Health Conference in Bangkok, Thailand on

the "Longitudinal evaluation using the recently developed Defense Automated Neurobehavioral Assessment (DANA) tool of the cognitive impact of Electroconvulsive Therapy (ECT) in the treatment of Major Depressive Disorder (MDD)"
- Presented poster at the 2014 Military Health Systems Research Symposium (MHSRS). ***(Appendix G)***
- Poster presented to Johns Hopkins University School of Medicine Psychiatry Research Symposium.
- Presented abstract on October 20, 2014 to the Health Information Technology Conference in Baltimore, MD. ***(Appendix K)***
- Preparing manuscript on initial findings of correlation between DANA and the Mini Mental Status Exam (MMSE). (***Preliminary analysis in Appendix O)***

3. VA PTSD Study (Project #: 2013-03/JLS/PROMISE0007)

- Obtained normative data using DANA on 73 older and female veterans in August/September 2014.
- Longitudinal data for 48 completed participants received by HBTMH research team and extracted from devices for analysis. 28 participants completed 3 DANA assessments; 9 participants dropped out after 2 assessments, and 11 only completed one assessment.
- Cleaned, coded, and formatted data for input into SPSS for data analysis.
- Analysis of data and manuscript preparation is underway. (***Interim analysis in Appendix Q, slides "Interim Analysis" through "Next Steps").***
- Ran data analysis measures on DANA for test reliability (test-retest, split half, alpha correlations), internal validity (factor analysis), as well as sensitivity and specificity (ROC and logistic regression).

Additional Completed Data Analysis:

Of the data analysis below, no human subjects research was conducted under this RIF project. The data overview below was implemented under other funding during the period of the RIF and is included as a reference point for further validation of DANA.

Mixed Martial Arts (MMA) Data:

- Data for 19 MMA athletes were collected. The goal of this data collection was to compare subjects with multiple concussions (MMA) vs. those with acute concussion. An exploratory analysis was completed. (***Report in Appendix R).***

Air Force Academy Football Data:

- Data for 153 healthy Football Athletes were collected along with 6 concussed. The goal of this data collection was to examine what the patterns of acute concussion data were over time. (***Report in Appendix S).***

In-Theater Afghanistan Data Analysis (DANA vs. ANAM):

- An analysis was completed for the ANAM test battery against DANA. The goal of the analysis was to understand how DANA measures differ from ANAM measures on similar sub-tests. (***Report in Appendix T).***

Altitude Data Analysis:

- Study comparing cognition at different altitudes using DANA (***Analysis in Appendix U).*** For additional details please see publications titled "*AltitudeOmics: the integrative physiology of human acclimatization to hypobaric hypoxia and its retention upon renascent*" ***(Appendix B)*** and "*AltitudeOmics: Decreased reaction time after high altitude cognitive testing is a sensitive metric of hypoxic impairment*". ***(Appendix C)***

Power Analysis Calculations for Normative Data:

- Normative data collection power analysis done to identify number of subjects needed to collect for reference normative database. (***Appendix V)***

Task 5: Reporting

DANA includes an on-screen reporting feature for users as well as in-depth exporting report functionality for researchers that includes detailed trial-by-trial information for further statistical analysis. Both on-screen and detailed report formats are generally specific to the user community's need (e.g. clinical, military, etc.). For each community, customization may be needed to provide the most optimal information required for their specific use. The current DANA reporting function is generalized since an end user has not been finalized; our general reports are based off interviews with a number of clinicians as well as extensive feedback received from our partners who are currently using DANA. Once we have identified our target transition partner and are ready to facilitate the final format, we will ensure expert feedback and assessment of the ease of understanding the reports that are generated.

Also in this reporting period, we worked with the Federal Interagency Traumatic Brain Injury Research (FITBIR) informatics system to get our data in the correct format for upload. FITBIR was designed by the NIH and Department of Defense to facilitate research and create an environment for collaboration.

Because DANA RIF is a DOD-funded grant, we were to upload the data collected from the Concussion Study (UW) to the FITBIR database. We have completed the creation of our FITBIR account, have worked with them on drafting the structure of our data template, and have completed upload of the data from the UW study.

Database Outcomes:

The AnthroTronix in-house database called, ``research'' houses all data directly and indirectly relating to the DANA project. It is a MySQL relational database that provides the capability to link together various types of data contained within it. ``Research'' holds both cognitive and psychological test information, by summary and by trial. ***(Database diagram in Appendix M)***

Additionally, in order to streamline data analysis, we developed a way automatically parse and clean data. We first developed routines by subtest that would take large files of data and separate them into information-by-subject, compute the necessary and widely used summary statistics, and also flag subjects who performed sub-par due to issues such as malingering; this automation process rendered files that were readied for easy export into the database. When in the database, it can be accessed easily, and each type of metric can be related to other types of metrics.

A relational database is object-constructed – categorically, not hierarchically. The contents of a relational database are as follows:

Tables "Relations" that metaphorically represent objects contained therein by tabular format. A table is an implementation of a "base relation," signifying that data is stored for access.

Columns Fields of a record, or in database vocabulary, "attributes."

Rows Data value records or "tuples."

Views Other types of relations that represent objects contained therein by tabular format, but a view is an implementation of a "derived relation," signifying that data is not stored for access, but rather acts as a single relation resulting from enactment of a pre-constructed query; essentially, a view provides in one place information gathered from many tables, without utilizing the permanent storage space of the database. Every view in "research" is designated with an ending letter, "q".

The MySQL Workbench application allows one to visually structure a database or schema, with the use of an enhanced entity-relationship (EER) diagram. ***(DANA EER in Appendix M)***

Task 6: Transition DANA for Deployment

Task 6A: Prepare and File FDA 510(k); Task 6B: Implement Quality System processes per FDA 21 CFR Part 820; Task 6C: Software Documentation for 510(k) application; Task 6D: Literature Review of pre 1976 Test Artifacts; Task 6E: Additional Documentation in Support of 510(k) Application

In order for DANA to transition for use by the DOD, it needed to be reviewed and cleared by the FDA as a mobile medical device. To that end, we submitted a 513(g) application to the FDA requesting determination as to its classification, i.e., Class I, II or III in April 2013. We received feedback from the FDA regarding our 513(g) application, and the FDA's response was that DANA was to be considered a Class III device subject to a 510(k) application. Due to this classification we moved ahead with working on a 510(k) application, which was completed and submitted in July 2014. The FDA determined that DANA was an unclassified device, and we received FDA clearance on October 15, 2014. ***(Clearance Letter in Appendix X)***

During the process of submitting a 510(k) to obtain FDA clearance, ATinc worked with the FDA to provide sufficient information and documentation on DANA and to make sure DANA met the necessary criteria for clearance. There were several steps taken as part of this process. We found a predicate device—the QB Test—that best matched the intended use of DANA and could be compared to as part of the 510(k). Both DANA and the QB Test are Mobile Based Task Performance Recorders, DANA because it measures reaction time on a mobile platform.

Furthermore, we restructured our software quality process to match the guidelines set out by the FDA. We also discussed how to classify DANA with the FDA; it was originally considered a Class III, but we proved that high of a class not to be necessary (of low risk, etc.), and DANA is currently unclassified. We analyzed the safety risks and hazards of DANA and made sure they were within acceptable limits. This was a process of testing and evaluating the software, determining its level of concern (minor), and documenting all testing and results as well as corrective measures and design elements that mitigate or eliminate said risks and hazards. DANA was found to have few hazards and risks associated with it. In addition, we created labeling stating the indications of use and providing instructions elucidating those indications that met FDA requirements for labeling.

Outcomes:
Obtaining clearance attests that DANA is a safe and effective device. As part of our FDA 510(k) application, we developed extensive supporting documentation; the documents are outlined below. DANA receiving FDA clearance ***(Appendix X)*** confirms the value of DANA as a neurocognitive assessment tool for use by medical personnel.

510(k) premarket notification—demonstrates that the device to be marketed is at least as safe and effective, that is, substantially equivalent, to a legally marketed device. Ours included the following sections:

- Medical Device User Fee Cover Sheet (Form FDA 3601)
- CDRH Premarket Review Submission Cover Sheet
- 510(k) Cover Letter
- Indications for Use Statement
- 510(k) Summary or 510(k) Statement—brief summary of the device included in the 510(k) and the supporting information.
- Truthful and Accuracy Statement—statement certifying that all information submitted in the 510(k) is truthful and accurate and that no material fact has been omitted.
- Executive Summary—concise description of the device, including the indications for use and technology; device comparison table; concise summary for any performance testing in the submission.
- Device Description—performance specifications and brief description of the device design requirements.
- Substantial Equivalence Discussion—identify the predicate device; provide a detailed comparison with our device in terms of indications for use, technology and performance specifications. Our predicate device was the QB Test.
- Software—appropriate software documentation; identification of the "level of concern" and documentation thereof. A Safety Risk Analysis document was developed that provides a comprehensive assessment of potential hazards that may occur in the use of DANA. Contains descriptions of Risk Rating Criteria, Modes of Control and Document References. Also includes the Safety Risk Analysis Table and Safety Requirements by mode of control. This is proprietary information and thus, not included in this report.
- Indications for Use
  Identification and description of the specific indications for use statement for the device(s). It identifies the target population in a significant portion of which sufficient valid scientific evidence has demonstrated that the device as labeled will provide clinically significant results and at the same time does not present an unreasonable risk of illness or injury associated with the use of the device.
- Software Documentation
  The software documentation for the FDA clearance is proprietary and therefore not included in this report.
- Standard Neuropsychological Questionnaires
  Full text and scoring info for neuropsychological questionnaires that are included in DANA (e.g. PHQ-8).
- Proposed Labeling
  Labeling" includes the device label, instructions for use, and any patient labeling.

The labeling for the FDA clearance is proprietary and therefore not included in this report.

Other Transition Activities

A number of paths exist for this transition, and our first success to date is with the Neurocognitive Assessment, Rehabilitation and Reintegration Product Line, UNITED STATES ARMY MEDICAL COMMAND. Dr. Michael Russell, the ANAM Program Director, and his successor, Dr. Watson, have commissioned DANA for a norming study they are conducting for the US Army. To date, data from 824 subjects has been collected. We now have norms for the age bins of 18-19, 20-24, 25-29, 30-34, 35-44, 45-54, and 55-64.

In addition, we have offered to work closely with an integrated product team (IPT), headed by Dr. Valerie Trabosh and LTC Atchison at MRMC, specifically set up for this purpose, and we await the IPT's guidance and direction. As of this final report LTC Atchison had introduced ATinc to the US Army Rapid Equipping Force, and we were ready to submit DANA to an interoperability network study, but REF delayed that opportunity.

Similarly, we discussed the development of a "performance app", based on a subset of DANA tests, to be distributed through DARPA's Transformative Apps program, but further progress on that front will depend on identifying a customer and a set of requirements.

Also with DARPA's help, we submitted a DANA Android application package file (APK) for them (DARPA) to review. It is necessary for DARPA to "clear" or "vet" DANA software for hosting on military computer systems. Since the DARPA secure kernel was developed by a contractor, Invincea, the operating system is proprietary, and we have invited the program manager to install the DARPA kernel on our devices so that we can be assured that device timing is not negatively impacted. As of this final report there are no updates from DARPA.

We completed a research and interview campaign targeting opportunities within the U.S. Department of Defense and the U.S. Intelligence Community (including DHS, State) with need and budget for Traumatic Brain Injury assessment and monitoring. Similarly, we compiled research and inquiries into an unclassified opportunity report that will help with DANA commercialization and new product market entry.

Task 7: DANA Reliability and Validity Publications

To further verify the reliability and validity of DANA, we developed a trade study reflecting the work done to address questions regarding the sensitivity, specificity and discriminative validity of DANA.

During the course of this RIF contract, we have been able to publish our findings in a variety of journal publications. The manuscripts resulting from our research in the past 2 years are listed under the "Products" section of this report starting on page 14.

Conclusions

All studies have completed data collection. Data analysis and manuscript preparation are currently underway. Ongoing analysis shows promise regarding DANA's applicability, in part because several key areas important to DANA's usability in CONUS, including depression, concussion, and clinical treatment populations, are being looked at. We will be presenting a poster on ongoing validation of DANA with Fort Hood norms at this year's Military Health Systems Research Symposium.

Partnering with other institutions has aided us in fulfilling both the transition and science efforts. DANA data was successfully integrated with FITBIR, and we submitted the DANA

Android application package file (APK) to DARPA for vetting. Our studies were conducted in collaboration with several prestigious organizations whose interest in DANA demonstrated its value, and the data collected by will help prepare DANA for CONUS clinical use.

Under this Rapid Innovation Fund Contract, ATinc received significant feedback and input from Dallas Hack, COL (Rtd) USA, who recently retired the Brain Health Program Coordinator in the Office of the Principal Assistant for Research & Technology, US Army Medical Research and Material Command (MRMC). ATinc also briefed DANA to the Integrated Product Committee within MRMC that has responsibility for this area. ATinc has also briefed other key stakeholders, including the following individuals, as well as others:

- John E. Meyers, Psy.D.; ANAM Program Director/Chief Neurocognitive Assessment Branch Rehabilitation and Reintegration Division, HQDA, Office of the Surgeon General of the Army
- COL Sidney Hinds, MD; National Director, Defense and Veteran's Injury Brain Center (DVBIC),
- Ms. Kathy Helmick; Deputy Director, DVBIC
- LTC Eugene Kim, MD; Command Psychiatrist, United States Army Special Operations Command (USASOC)
- CAPT Jack Tsao, MD, USN: Director, Traumatic Brain Injury Programs, Wounded, Ill & Injured Directorate, US Navy Bureau of Medicine and Surgery.

At the 2015 Military Health Systems Research Symposium (MHSRS), DANA was cited by RADM Bruce Doll, USN, who is dual-hatted as the Director, Research, Development and Acquisition, Defense Health Agency and as Deputy Commander, US Army MRMC, and by Dr. David Smith, the Deputy Assistant Secretary of Defense for Force Health Protection and Readiness, ***as a key success.*** In addition, representatives from AnthroTronix met with MAJ Walter Carr, USA and Dr. John Myers to discuss possible transition opportunities.

What opportunities for training and professional development has the project provided?
Nothing to Report.
How were the results disseminated to communities of interest?
Related to the results of this effort, we have published 5 papers and plan to publish several more. DANA was utilized in 5 posters that were presented at MHSRS, in another for the John Hopkins University School of Medicine Psychiatry Research Symposium, and an abstract that was presented to the Health Information Technology Conference in Baltimore, MD. AnthroTronix has also reported quarterly to the MRMC and briefed DANA to the IPT within the MRMC as well as to other relevant organizations and persons *(**see Conclusions, p. 13**).*
What do you plan to do during the next reporting period to accomplish the goals?
Nothing to Report as the project has ended. However, we plan to publish results as reports are finalized.
IMPACT:
What was the impact on the development of the principal discipline(s) of the project?
DANA has great potential to provide a better way for health practitioners and cognitive researchers to evaluate cognition and to track it over time. The JHU preliminary data analysis shows that DANA provides more cognitive sensitivity than the MMSE in a clinical population diagnosed with major depressive disorder ***(See "Results" slide through "Sample Patient #2" in Appendix L).*** Our PTSD study showed that DANA could be used to track cognition over time in a home based telehealth model, and UW preliminary findings

show that the DANA Spatial sub-test may be sensitive to concussion ***(See tables "Baseline (controls) vs. 45 Day(concussed) meanThru", "Baseline (controls) vs. 15 day (concussed) meanThru", ", "Baseline (controls) vs. 15 day (concussed) meanRT", "Baseline (controls) vs. 24 hour (concussed)","**, and ***"Baseline (controls) vs. 8 Day (concussed) percent Correct" in Appendix N).***

What was the impact on other disciplines?
Nothing to Report.

What was the impact on technology transfer?
One of the objectives of this project was to transition DANA to the military. We have made great strides in paving the way for DANA to be transitioned to DoD as per the activities listed in Task 6 and other transition activities. In addition, there is great interest in the clinical health market for DANA based on findings from the JHU study. AnthroTronix will continue to pursue transfer activities beyond the military.

What was the impact on society beyond science and technology?
DANA is the first and currently the only NCAT to have received FDA clearance. DANA's clearance is a significant step forward for healthcare providers' ability to treat patients, because there are very few tools that clinicians and other health providers can use to track changes or find impairments in cognitive functioning and no others that are FDA-cleared. With clearance and the scientific development under this effort, DANA's ability to be used in acute and non-acute settings to identify neurocognitive issues, isolate symptoms, and inform the proper treatment has expanded.

CHANGES/PROBLEMS:
Changes in approach and reasons for change
While the original proposal called for a scientific thrust that would track a deployed battalion OCONUS longitudinally over time, MRMC leadership (Colonels Castro and Hack) agreed that the statement of work be modified to concentrate on CONUS-based studies such as testing DANA in clinical drug, fatigue/alertness, concussion and/or depression protocols.
Actual or anticipated problems or delays and actions or plans to resolve them
A delay in data analysis will require additional publications to be completed this coming year. AnthroTronix is committed to publishing all results from these studies using IRAD funds.
Changes that had a significant impact on expenditures
Nothing to Report.
Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
Nothing to Report.
Significant changes in use or care of human subjects
Nothing to Report.
Significant changes in use or care of vertebrate animals –N/A
Significant changes in use of biohazards and/or select agents –N/A

PRODUCTS:
Publications, conference papers, and presentations, **journal publications**
2013:

Lathan, Corinna, et al. "Defense Automated Neurobehavioral Assessment (DANA)-psychometric properties of a new field-deployable neurocognitive assessment tool." Military medicine 178.4 (2013): 365-371.

Published: Yes*. Acknowledgement of federal support:* Yes

Describes the psychometric properties of DANA, based on the assessment of 224 service members under various environmental stresses: extreme cold, humidity, altitude, dry heat, and unstable platform conditions. DANA results were compared to data previously published from the currently used Automated Neuropsychological Assessment Metrics (ANAM) tool. DANA performed well in all five environments; test-retest reliability for subtests were within acceptable ranges; and stability was consistent with ANAM's.

2014:

Subudhi, Andrew W., et al. "AltitudeOmics: the integrative physiology of human acclimatization to hypobaric hypoxia and its retention upon reascent." PloS one9.3 (2014): e92191.

Published: Yes*. Acknowledgement of federal support:* No

Subjects were tested near sea level then at different altitudes. They were tested at an altitude of 5260m, and then retested at that altitude after being acclimatized to a lower altitude. 7 of the volunteers stayed at a lower altitude for 21 days, while 14 stayed for 7 days. Afterwards, the subjects were tested again at the high altitude.

Five of the DANA tests showed significantly worse scores upon arrival at 5260m and, for the subjects that reascended after seven days, two tests showed retention of acclimatization.

Roach, Emma B., et al. "AltitudeOmics: Decreased reaction time after high altitude cognitive testing is a sensitive metric of hypoxic impairment."NeuroReport 25.11 (2014): 814.

Published: Yes*. Acknowledgement of federal support:* Yes.

DANA was used to examine healthy volunteers at sea level and in hypoxic environments. It was administered three times: at sea level, when the subjects arrived at the destination altitude of 5260m, and after 16 days of acclimatization. There was a significant decrease in performance between sea level and the other tests. The SRT change score was measured (difference between two reaction time scores which reflects the mental effort spent). This score provides a more reliable indication of hypoxia-induced cognitive impairment than typical baseline procedures.

Spira, James L., et al. "The Impact of Multiple Concussions on Emotional Distress, Post-Concussive Symptoms, and Neurocognitive Functioning in Active Duty United States Marines Independent of Combat Exposure or Emotional Distress." Journal of neurotrauma 31.22 (2014): 1823-1834.

Published: Yes*. Acknowledgement of federal support:* Yes.

Examines whether concussions had a sustained impact on emotional and cognitive functioning of US Marines. 646 Marines were tested using the Standard battery.

Findings indicated that recent concussions were associated with more distress and that having three or more lifetime concussions was linked with the worst scores for depression, PTSD, anger, post-concussive symptoms, and the worst performances on simple cognitive tasks. DANA was sensitive to factors, showing that it has promise as a tool for detecting changes in cognitive functioning.

2015:

Russo, C. R., and C. E. Lathan. "An Evaluation of the Consistency and Reliability of the Defense Automated Neurocognitive Assessment Tool." Applied Psychological Measurement (2015): 0146621615577361
Published: Yes*. Acknowledgement of federal support:* Yes.
Examines Rapid test battery consistency in a US Air Force Academy football player population, who were tested before, during and after the football season. The study evaluates the stability of the test and describes an approach to determine reliability in terms of a "minimum difference" threshold for the detection of significant change. Study results indicated that the test results are consistent as long as the re-test session is administered within six months of the first session.

Books or other non-periodical, one-time publications.
Nothing to report.

Other publications, conference papers, and presentations.
2014
Eonta, S.E., Paech, G.M., Banks, S., Johnson, K., Della Vedova, C., Kamimori, G.H. (2014, August). *Impact of Caffeine on Neurocognitive Performance During Sleep Deprivations Using the Defense Automated Neurobehavioral Assessment (DANA)*. Poster Presented at the Military Health System Research Symposium, Ft. Lauderdale, FL.

Woods, S.R., Lathan, C., Susukida, R., Riehm, A., Askew, H., Rahn, K., Kaplin, A. (2014, August). *Longitudinal Evaluation Using the Recently Developed Defense Automated Neurobehavioral Assessment (DANA) Tool of the Cognitive Impact of Electroconvulsive Therapy (ECT) in the Treatment of Major Depressive Disorder (MDD).* Poster presented at the Military Health System Research Symposium, Ft. Lauderdale, FL.

Spira, J.L., King, L.A., Lathan, C., Tsao, J. (2014, August) *Development of an Objective, Functional Biomarker of Invisible Wounds of War for Use by Providers*. Poster Presented at the Military Health System Research Symposium, Ft. Lauderdale, FL.

2015
Kamimori, G.H., LaValle, C., Paech, G., Johnson, K., Banks, S., Dark, H., Eonta, S. (2015, August). *Performance on the Defense Automated Neurobehavioral Assessment Battery (DANA) and Simulated Driving Performance over 50h of Continuous Wakefulness: Correlation between Neurocognitive and Operational Performance (#2003).* Poster Presented at the Military Health System Research Symposium, Ft. Lauderdale, FL.

Lathan, C., Wallace, R., Shewbridge, R. (2015, August). *Differences in Cognitive Efficiency In Active Duty Military – Healthy vs. Those with Sleep Disturbance, Depression, and/or PTSD Using the DANA Automated Neurocognitive Assessment (DANA) Tool*. Poster Presented at the Military Health System Research Symposium, Ft. Lauderdale, FL.

Website(s) or other Internet site(s)
Nothing to Report.

Technologies or techniques
Nothing to Report.

Inventions, patent applications, and/or licenses

- Provisional patent application: 61/597,068, Performance Assessment Tool 02/09/2012
- Non-provisional patent application: US 13/764,162, Performance Assessment Tool 02/09/2012

Other Products
Nothing to Report.

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS
What individuals have worked on the project?

Name:	Dr. Corinna Lathan
Project Role:	Principal Investigator
Nearest person month worked:	6
Contribution to Project:	Dr. Lathan interfaced with Drs. Spira and Bleiberg during data management and reporting and supported the ATinc team of managers and engineers throughout the project during technical development.
Name:	Akhila Ananthram
Project Role:	Research Assistant
Nearest person month worked:	1
Contribution to Project:	Ms. Ananthram supported Ms. Shewbridge on all research efforts.
Name:	James Drane
Project Role:	Mechanical Engineer
Nearest person month worked:	11
Contribution to Project:	Mr. James Drane assisted in the coordination of the team, project management, technical assistance, integration, and mechanical engineering support for DANA.
Name:	Jonathan Farris
Project Role:	Software Engineer
Nearest person month worked:	8
Contribution to Project:	Mr. Farris led the programming and testing teams and coordinated programming. He assured both adherences to project timeline and for milestones, as well as quality assurance.
Name:	Patrick Gookin
Project Role:	Software Engineer
Nearest person month worked:	1
Contribution to Project:	Assisted Mr. Farris in software engineering tasks.
Name:	Clifford Knoll
Project Role:	Software Engineer
Nearest person month worked:	10
Contribution to Project:	Mr. Knoll contributed Android programming expertise and worked on DANA software development.
Name:	Joli Rightmyer
Project Role:	Mechanical Engineer
Nearest person month worked:	1
Contribution to Project:	Ms. Rightmyer provided integration support for DANA as well as testing and evaluation of technical functionality.

Name:	Dr. Emma Roach
Project Role:	Research Scientist
Nearest person month worked:	4
Contribution to Project:	Dr. Roach conducted data analysis and paper writing.
Name:	Kyle Rohrbach
Project Role:	Mechanical Engineer
Nearest person month worked:	5
Contribution to Project:	Mr. Rohrbach provided testing and evaluation of technical functionality.
Name:	Dr. Clementina Russo
Project Role:	Research Scientist
Nearest person month worked:	5
Contribution to Project:	Dr. Russo conducted data analysis and paper writing.
Name:	Charlotte Safos
Project Role:	Program Director
Nearest person month worked:	6
Contribution to Project:	Ms. Safos supported Dr. Lathan in the coordination of staff and overseeing general project and study management.
Name:	Alicia Salvino
Project Role:	Research Assistant
Nearest person month worked:	2
Contribution to Project:	Ms. Salvino supported Ms. Shewbridge on research efforts.
Name:	Rita Shewbridge
Project Role:	Project Manager
Nearest person month worked:	14
Contribution to Project:	Ms. Shewbridge supported Dr. Lathan and Ms. Safos on project management for DANA and coordinated research studies.
Name:	Jack Vice
Project Role:	Software Engineer
	2
	Mr. Vice provided senior level expertise in support of the operational use and testing of DANA
Name:	Dr. Lawrence Wolpert
Project Role:	Director of Research
Nearest person month worked:	19
Contribution to Project:	Dr. Wolpert led all DANA research and FDA approval efforts.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
Nothing to Report.

What other organizations were involved as partners?
Organization Name: University of Wisconsin (UW)
Location of Organization: Madison, Wisconsin
Partner's contribution to the project: Collaboration

Organization Name: VA Pacific Island Health Care System (Home-Based Telemental Health

(HBTMH)
Location of Organization: Honolulu, Hawaii
Partner's contribution to the project: Collaboration

Organization Name: US Army Medical Research and Material Command (MRMC)
Location of Organization: Fort Detrick, Maryland
Partner's contribution to the project: Collaboration, other

Organization Name: United States Army Medical Command
Location of Organization: San Antonio, Texas
Partner's contribution to the project: Collaboration.

Organization Name: Defense Advanced Research Projects Agency (DARPA)
Location of Organization: Arlington, Virginia
Partner's contribution to the project: Other.

Organization Name: John Hopkins University (JHU)
Location of Organization: Baltimore, Maryland
Partner's contribution to the project: Collaboration.

Organization Name: Walter Reed Army Institute of Research (WRAIR)
Location of Organization: Silver Spring, Maryland
Partner's contribution to the project: Collaboration.

Organization Name: Pacific Health Research and Education Institute (PHREI)
Location of Organization: Honolulu, Hawaii
Partner's contribution to the project: Collaboration.

Organization Name: Federal Interagency Traumatic Brain Injury Research (FITBIR)
Location of Organization: Bethesda, Maryland
Partner's contribution to the project: Other.

SPECIAL REPORTING REQUIREMENTS
COLLABORATIVE AWARDS: None.
QUAD CHARTS: Appendix W
APPENDICES:

- DANA Publications
    - *Appendix A*: Defense Automated Neurobehavioral Assessment (DANA)—Psychometric Properties of a New Field-Deployable Neurocognitive Assessment Tool
    - *Appendix B*: AltitudeOmics: The Integrative Physiology of Human Acclimatization to Hypobaric Hypoxia and Its Retention upon Reascent
    - *Appendix C*: AltitudeOmics: Decreased reaction time after high altitude cognitive testing is a sensitive metric of hypoxic impairment
    - *Appendix D*: The Impact of Multiple Concussions on Emotional Distress, Post-Concussive Symptoms, and Neurocognitive Functioning in Active Duty United States Marines Independent of Combat Exposure or Emotional Distress
    - *Appendix E*: An Evaluation of the Consistency and Reliability of the Defense Automated Neurocognitive Assessment Tool

- Abstract and Poster Presentations
    - MHSRS Posters from 2014
        - *Appendix F*: Impact of Caffeine on neurocognitive performance during sleep deprivation using the DANA.
        - *Appendix G*: Longitudinal evaluation using the recently developed DANA tool of the cognitive impact of Electroconvulsive Therapy (ECT) in the treatment of major depressive disorder.
        - *Appendix H*: Development of an objective, functional biomarker of invisible wounds of war for use by providers.
    - MHSRS Posters from 2015
        - *Appendix I*: Performance on the DANA and simulated driving performance over 50h of continuous wakefulness: Correlation between Neurocognitive and Operational Performance.
        - *Appendix J*: Differences in cognitive efficiency in active duty military – Healthy vs. those with sleep disturbance, depression, and/or PTSD using the DANA tool.
    - *Appendix K*: Health Information Technology Conference Abstract on JHU Study.
- Meeting Briefings
    - *Appendix L*: DANA Briefing March 2015
- Database Documentation
    - *Appendix M*: Database Diagram
- Supporting Data for RIF Studies
    - UW Study
        - *Appendix N*: University of Wisconsin—Brief Report
    - Depression Study
        - *Appendix O*: ECT Statistics (DANA vs. MMSE)
        - *Appendix P*: ECT Study Tables
    - PTSD Study
        - *Appendix Q*: Home-Based TeleMental Health for Rural Veterans
- Additional Data Analysis
    - *Appendix R*: Analysis of Defense Automated Neurobehavioral Assessments on Two Groups of Mixed Martial Arts Fighters
    - *Appendix S*: Air Force Academy Football Data
    - *Appendix T*: In-Theater Afghanistan Data Analysis (DANA vs. ANAM)
    - *Appendix U*: Altitude Data Analysis
    - *Appendix V*: Power Analysis Calculations for Normative Data
- *Appendix W*: Quad Chart
- *Appendix X*: FDA Clearance Letter

Appendix A

ORIGINAL ARTICLES

Authors alone are responsible for opinions expressed in the contribution and for its clearance through their federal health agency, if required.

MILITARY MEDICINE, 178, 4:365, 2013

Defense Automated Neurobehavioral Assessment (DANA)—Psychometric Properties of a New Field-Deployable Neurocognitive Assessment Tool

Corinna Lathan, PhD; James L. Spira, PhD, MPH†; Joseph Bleiberg, PhD‡; Jack Vice*; CAPT Jack W. Tsao, USN§*

ABSTRACT The Defense Automated Neurobehavioral Assessment (DANA) is a new neurocognitive assessment tool that includes a library of standardized cognitive and psychological assessments, with three versions that range from a brief 5-minute screen to a 45-minute complete assessment. DANA is written using the Android open-source operating system and is suitable for multiple mobile platforms. This article presents testing of DANA by 224 active duty U.S. service members in five operationally relevant environments (desert, jungle, mountain, arctic, and shipboard). DANA was found to be a reliable instrument and compared favorably to other computer-based neurocognitive assessments. Implications for using DANA in far-forward military settings are discussed.

INTRODUCTION

In January 2009, the U.S. Navy Bureau of Medicine and Surgery identified a need to enhance existing battlefield concussion assessment and requested the development of a durable, portable, and field-hardened neurocognitive assessment tool (NCAT) to provide a practical means to conduct neurocognitive and psychological assessment in field deployment settings. The purpose of combining neurocognitive and psychological assessment was to permit more comprehensive evaluation of the broad range of problems that may be encountered during combat deployment. This article describes the resulting NCAT, Defense Automated Neurobehavioral Assessment (DANA); DANA's psychometric properties based on assessment of 224 active duty U.S. service members under challenging field conditions; and presents comparisons to published NCAT data.

DANA consists of three test batteries of different durations and compositions designed for increasingly detailed assessment (Table I). The three batteries include (1) DANA Rapid, a 5-minute battery of three basic reaction-time measures; (2) DANA Brief, a 15-minute test that includes DANA Rapid plus additional neurocognitive tests as well as psychological screening tools for post-traumatic stress disorder (PTSD), depression, and insomnia; and (3) DANA Standard, a 45-minute more comprehensive battery of neurocognitive and psychological tests. This hierarchical set of batteries is designed to facilitate health care providers' access to standardized, reliable, and valid objective and subjective measures. DANA's portability, multiple test batteries, and user-friendly interface enable its use by a wide range of health care providers, from frontline medics/corpsmen to licensed health care professionals.

Establishing reliability and feasibility of this platform in a military population is necessary before attempting clinical validation and utilization. The eventual goal of DANA is to assist clinicians to (a) make rapid and accurate assessment of cognitive and psychological dysfunction secondary to brain injury and/or the psychological wounds and stressors of war,

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The preliminary data of this article, "Defense Automated Neurobehavioral Assessment (DANA): A Field-Deployable Tool for Assessing Concussion and Deployment Stress," was presented as an oral presentation by the authors J.L.S., C.L., J.B., and J.W.T. at the Military Health System Research Symposium (MHSRS) Conference, Fort Lauderdale, FL, August 2012.

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TABLE I. DANA Test Batteries*

DANA Rapid (5 Minutes)	DANA Brief (15 Minutes)	DANA Standard (45 Minutes)**
Simple Reaction Time (SRT)	SRT	SRT
Procedural Reaction Time (PRO)	Code Substitution Simultaneous (CDS)	CDS
Go/No-Go (GNG)	PRO	PRO
	Spatial Discrimination (SPD)	SPD
	GNG	GNG
	Code Substitution Delayed (CDD)	CDD
	SRT	Matching to Sample (MSP)
	Patient Health Questionnaire (PHQ)	Sternberg Memory Search (STN)
	Primary Care PTSD Screen (PC-PTSD)	SRT
	Insomnia Screening Index (ISI)	Combat Exposure Scale (CES)
		PHQ
		Pittsburgh Sleep Quality Index (PSQI)
		PTSD Checklist—Military Version (PCL-M)
		Deployment Stress Inventory (DSI)

*For detailed test descriptions, see Table AI. **MSP and STN were still under development at the time of this testing and so are not included in the results.

(b) facilitate referral to treatment for wounded service members, (c) monitor recovery, and (d) aid in return-to-duty determination. Thus, DANA is intended to enhance military capability and better ensure a healthy fighting force.

METHODS

DANA Platform

DANA is a Java-based mobile application that runs on an Android operating system. The primary advantages of Android are that it is open source, open license (Apache 2.0), well supported and based on a Linux kernel, which is nearly ubiquitous. Java has the advantage of being a high-level, class-based, object-oriented language designed as a "write once, run anywhere" solution and thus is portable across a wide range of devices and desktops. DANA, therefore, can run on any Android mobile device and can be used with a stylus or touch screen.

Based on the Navy Bureau of Medicine and Surgery, requirements for MIL-SPEC commercial-off-the-shelf hardware, we conducted a comprehensive trade study and selected the Trimble Nomad, the military-grade-hardened handheld computer used in the current study. A Tektronix 100 MHz analog to digital (ADC) oscilloscope was used to test the input variability of device hardware and device software that could contribute to the overall response times. A push action switch was connected to the ADC, which was then used as the input stylus on the Nomad to measure RT. The interval between two inputs as recorded by DANA and by the ADC was compared over 10 trials. The average difference was 6.8 milliseconds with a standard deviation (SD) of 3.7 milliseconds. By comparison, the input variability with a Microsoft windows personal computer can range from 4–25 milliseconds.[1,2]

DANA Test Battery

Selection of the neurocognitive and psychological tests included in DANA was established by a tri-service, Veterans Administration, and civilian scientific advisory board that included military and civilian neuropsychologists and psychologists, neurologists, and corpsmen. All tests included in DANA's test batteries meet the requirements of the American Psychological Association's standard for tests and measurements and all tests are in the public domain. Eight cognitive tests and seven psychological questionnaires were selected (Table AI) and are divided into three test batteries, as shown in Table I. Tests were selected based upon their potential to address specific deployment-related concerns, such as concussion and combat distress or exhaustion. Although all tests utilized have an extensive literature regarding their reliability and validity, they have not been reported in this specific configuration nor implemented for service members in this manner. The advisory board also contributed to and provided feedback on the user interface design to ensure ease of use by multiple levels of caregivers including the corpsmen, general medical officers, and neuropsychologists.

Participants and Procedure

To evaluate the deployment feasibility of DANA, we recruited 224 active duty service members comprising 40 or more active duty military personnel in each of 5 diverse operational environments. No subjects were excluded, since all service members were fit for duty, not undergoing any disability evaluation, and thus assumed to be healthy. The purpose of assessing service members across diverse environmental conditions was to show the robustness of the hardware and software administration under different operational tempos and to identify any environmental concerns with the reliability of the instrument.

- — Arctic (Thule Air Force Base—Greenland in the winter)
- — Jungle (U.S. Marine Corps Jungle Warfare Training Center—Okinawa, Japan, in the summer)
- — Altitude (U.S. Marine Corps Mountain Warfare Training Center—Bridgeport, CA, approximately 3,000 m)
- — Desert (U.S. Marine Corps Desert Warfare Training Center—Twentynine Palms, CA, in the summer)
- — Shipboard (USS George Washington during high seas in the Western Pacific)

Device performance (e.g., battery life, display characteristics) was evaluated under the specific environmental conditions (e.g., humidity, temperature) through a minimum of 12-hour exposure. The only instrumentation reliability issue was a screen refresh rate delay in the Go/No-Go (GNG) test in the arctic environment. Because this screen rendering delay would affect test results, the rendering process software was redesigned, which successfully mitigated the delay.

The research protocol was approved by the AnthroTronix Institutional Review Board, the VA Institutional Review Board, and received a Department of the Navy Human Research Protections Program review. A letter was obtained from the commanding officer of each test facility and all subjects signed an informed consent document to participate in testing. On Day 1, each subject was tested on all three batteries, the DANA Rapid, Brief, and Standard. Subjects returned on Day 2 to repeat the sequence of batteries resulting in the following protocol:

— Day 1 (approximately 120 minutes)—Consent Process, DANA Rapid, DANA Brief, DANA Standard
— Day 2 (approximately 40 minutes)—DANA Rapid, DANA Brief, DANA Standard (cognitive tests only)

(The above times include 5-minute breaks between each battery.)

A research team of clinical psychologists and technical staff administered testing. Participants were instructed to hold the stylus about 1-cm above the screen, and to respond as rapidly and accurately as possible. All other instructions were embedded within the tests. To minimize learning and practice effects, test stimuli are generated at random and each test has practice trials before the actual test trials. Parameters of the final version of DANA's individual subtests are described in Table AII including each subtest's stimulus presentation duration, response interval, and interstimulus interval.

Data were analyzed in SPSSv20 for descriptive statistics, split-half reliability, test–retest reliability, and cross-test correlations. For internal consistency, we examined split-half correlations of the first and second half set of trials for the first administration of each test on each day. To evaluate test–retest reliability across administrations, we calculated intraclass correlation coefficients (ICCs)[3] that have been used to evaluate reliability for other health status instruments.[4] Because of multiple analyses, significance levels were set to between $p < 0.01$ and $p < 0.001$, depending upon the number

TABLE II. Descriptive Statistics for all DANA Variables for Each Administration

	Task	Administration	*n*	Median RT Correct ± SD		Average of Median Throughput ± SD		Percentage Correct ± SD	
1	SRT	1	223	309.7	±65.3	199.6	±33.4	99.7	±3.3
		2	223	309.3	±64.6	199.8	±34.6	99.5	±2.6
		3	220	300.6	±55.5	204.4	±33.8	99.4	±3.4
		4	213	302.0	±53.3	202.2	±33.4	99.3	±4.0
		5	212	308.3	±65.1	200.6	±36.7	99.3	±4.7
		6	172	298.4	±68.5	207.1	±31.7	99.7	±2.4
		7	172	307.8	±77.0	202.1	±35.7	99.4	±2.3
		8	164	305.1	±49.2	200.7	±30.6	99.6	±2.2
		9	122	317.9	±69.0	195.7	±37.5	99.7	±1.5
		10	121	310.7	±54.9	197.8	±30.7	99.8	±0.8
2	PRO	1	224	604.5	±101.6	100.1	±15.5	98.3	±4.3
		2	220	579.6	±91.4	103.8	±15.1	98.1	±4.0
		3	213	571.8	±84.8	104.8	±14.2	98.0	±4.0
		4	174	579.1	±79.9	103.6	±13.4	98.3	±3.1
		5	164	579.7	±95.4	104.1	±15.6	98.2	±3.5
		6	122	565.0	±84.1	105.7	±15.0	97.6	±5.3
3	GNG	1	214	535.4	±96.8	114.2	±18.5	99.1	±2.5
		2	214	519.3	±86.8	117.6	±18.5	99.3	±2.3
		3	193	520.0	±91.4	116.7	±19.9	98.2	±4.5
		4	163	527.2	±97.4	116.1	±19.2	99.0	±2.8
		5	99	506.4	±98.3	120.9	±20.8	98.8	±3.6
		6	75	521.0	±109.6	117.7	±21.7	98.4	±5.2
4	SPD	1	221	1690.2	±376.3	34.4	±7.1	92.8	±5.4
		2	209	1533.0	±361.5	37.3	±9.4	90.6	±5.7
		3	172	1562.3	±383.9	37.8	±9.6	93.1	±5.8
		4	119	1456.6	±311.4	38.2	±7.4	89.3	±6.2
5	CDS	1	223	1284.9	±277.7	47.5	±9.5	97.5	±3.1
		2	212	1256.7	±234.5	47.8	±8.9	96.8	±4.0
		3	171	1228.7	±257.0	49.8	±10.8	97.7	±3.1
		4	120	1193.4	±211.1	50.5	±9.4	97.3	±3.2
6	CDD	1	212	1046.7	±221.5	55.0	±11.9	92.1	±8.2
		2	190	1004.3	±183.1	56.2	±11.7	91.1	±9.1
		3	161	996.7	±184.2	56.8	±12.8	90.9	±9.5
		4	103	956.9	±157.4	59.6	±11.5	92.5	±7.9

TABLE III. Comparison to Previously Reported Data[a]

		DANA	ANAM (2006)	ANAM (2008)	ANAM (2012)
SRT	*n*	223	2,261	5,237	107,413
	Mean[a]	309.7	261.3	267	261
	SD	65.3	56.1	74	47
	Ratio	21.08%	21.47%	27.72%	18.01%
PRO	*n*	224	—	—	107,353
	Mean[a]	604.5	—	—	592
	SD	101.6	—	—	90
	Ratio	16.81%	—	—	15.20%
CDS	*n*	223	2,331	5,237	107,546
	Mean[a]	1284.9	1,191	1,096	1,162
	SD	277.7	248.7	265	272
	Ratio	21.61%	20.88%	24.18%	23.41%
CDD	*n*	212	1,891	5,202	107,523
	% Accuracy	92.1	88.7	86.30	90
	SD	8.2	9.3	15.80	11.4
	Ratio	8.90%	10.48%	18.31%	12.67%

[a]Medians are shown for DANA.

of analyses conducted to correct for type-1 error. Psychological measures were scored using conventional methods.

RESULTS

DANA performed well in all five field environments with no significant difference across data sets; therefore, the data for all five operational environments were combined. The number of total subjects for each test ranged from $n = 75$ to $n = 224$ depending on whether or not the service member was available to participate in all administrations across 2 days. All but one test (Code Substitution Delayed [CDD]) had over 200 subjects for at least two test administrations.

Scores on psychological measures revealed an overall psychologically healthy sample. Combat Exposure Scale (CES) was in the light range (3.7, with 17 indicating moderate exposure). PTSD Checklist—Military Version (PCL-m) (26), Patient Health Questionnaire (PHQ)-8 (4.6), Pittsburgh Sleep Quality Index (PSQI) (5.9), and Deployment Stress Inventory (DSI) (9.7) were each far below the score needed to reach clinical criteria.

Data exclusions included the elimination of trials with anticipatory responses and test administrations indicating random responses (criterion for exclusion was set at less than 65% correct—since tasks are binary, 50% correct represents random responding). No slow RT responses were eliminated, but to mitigate their undue influence we used medians rather than means to describe the data. Less than 1% of the response trials and less than 2% of the test administrations were eliminated based on these criteria. No subjects were eliminated from analysis based upon a criterion of having more than one test administration eliminated in a battery.

Table II shows the descriptive data for each administration of each test, and Table III compares DANA median RT and SD to previously published reports of mean data from the Automated Neuropsychological Assessment Metrics (ANAM, currently used by the U.S. Department of Defense for baseline, predeployment neurocognitive testing) in military personnel.[5–7] DANA uses median correct RT as the relevant metric, whereas ANAM reports means; however, because of the sample size and the normal populations assessed, the mean and median are assumed to be similar for ANAM.

Although not significantly different, absolute RT values may be different because of differing instrumentation (stylus versus mouse button) between ANAM and DANA. It is also possible to use the published ANAM data to calculate Coefficients of Variation (CVs) (ratio of RT to SD of RT) to show stability[8] and these are compared to analogous DANA subtests in Table III.

For reliability within administrations, split-half correlations of the odd–even trials are reported for the first administration of day 1 and day 2 for each test. Correlations were acceptably high ($p < 0.001$) and generally above 0.85—Simple Reaction Time (SRT) (0.91, 0.93), Procedural Reaction Time (PRO) (0.87, 0.86), GNG (0.85, 0.85), Code Substitution Simultaneous (CDS) (0.94, 0.93)—except for Spatial Discrimination (SPD) (0.76, 0.76) and CDD (0.76, 0.82). For test reliability across administrations, the ICC was calculated. The ICC for SRT was 0.95 indicating excellent reliability across the 10 administrations over 2 days. For PRO, GNG, SPD, and CDS, similar reliability was achieved with ICC values of 0.91, 0.95, 0.89, and 0.88, respectively. Only the CDD test did not have high reliability (0.54), which is expected for repeat CDD tests within a short time period because of the change in codes with each administration, resulting in proactive memory interference.

Correlations were also conducted between all psychological and cognitive measures. With the exception of CDD (difficulties using multiple administrations of this subtest because of memory interference were noted above), all cognitive subtests ($p < 0.001$) and psychological tests ($p < 0.001$) were correlated with each other; however, the psychological and cognitive tests did not correlate with each other in this

TABLE AI. DANA Test Descriptions

Test Name (Abbreviation)	Task Structure	Task Purpose
Simple Reaction Time (SRT)[a–c]	The subject taps on the location of the yellow asterisk symbol as quickly as possible each time it appears.	This task measures pure RT.
Procedural Reaction Time (PRO)[a–c]	The screen displays one of four numbers for 3 seconds. The subject presses on a left button ("2" or "3") or right button ("3" or "4") depending upon the number pressed.	A choice RT measure of accuracy, RT, and impulsivity. This choice RT task targets simple executive functioning with easy decision-making capabilities.
Go/No-Go (GNG)[a–c]	This is a forced choice RT task relevant to warfighters. A house is presented on the screen with several windows. Either a "friend" (green) or "foe" (white) appears in a window. The respondent must push a "fire" button only when a "foe" appears.	A choice RT measure of sustained attention and impulsivity. The test assesses speed and accuracy of targets, omissions, and commissions.
Spatial Discrimination (SPD)[b,c]	Pairs of four-bar histograms are displayed on the screen simultaneously, and the subject is requested to determine whether they are identical. One histogram is always rotated either ±90 degrees with respect to the other histogram.	Assesses visuospatial analytic ability.
Code Substitution Simultaneous (CDS)[b,c]	Subjects refer to a code set of 9 symbol-digit pairs that are shown across the upper portion of the screen. A sequence of single symbol-digit pairs is shown below the key, and the subject indicates whether or not the single pair matches the code by pressing Yes or No.	Assesses visual scanning and attention, learning, and immediate recall.
Code Substitution Delayed (CDD)[b,c]	After a delay of several intervening tests, the same symbol-digit pairs are presented without the code. The subject indicates whether or not the pairing was included in the code that was presented in the earlier code substitution learning section.	Assesses learning and short-term memory.
Sternberg Memory Search (STN)[c]	The subject memorizes a set of five letters, after which letters appear on the screen one at a time, and the subject determines if the letter on the screen is a member of the memory set.	Assesses working memory.
Matching to Sample (MSP)[c]	A single 4 × 4 checkerboard pattern is presented on the screen for brief study period. It then disappears for 5 seconds, after which two patterns are presented side-by-side. The subject indicates which of these two patterns matches the first.	A measure of short-term memory, attention, and visuospatial discrimination.
Insomnia Screening Index (ISI)[b]	A 5-item scale evaluating perceived insomnia severity and sleep habits. Each item is rated on a 5-point scale (0–4).	The total score ranges from 0 to 28 and higher scores indicate more severe insomnia. A cutoff score of 10 has been shown to indicate insomnia.[11]
Primary Care PTSD Screen (PC-PTSD)[b]	Four screening questions designed for use in clinical settings to screen for PTSD, with 3 out of 4 endorsed items suggestive of likely PTSD.	Questions assess hyper-arousal, re-experiencing, and avoidance for PTSD screening. This test is more sensitive than specific, but correlates highly with the PCL.[12,13]
Patient Health Questionnaire (PHQ)[b,c]	A 9-item depression scale assessing symptom severity and diagnostic criteria for major depressive disorder. For research purposes, item no. 9 (concerning suicide) was not included, yet research indicates that the scoring, reliability, and clinical validity are almost identical.	A score of 0–9 is likely to have no depression, 10–14 mild depression, 15–19 moderate depression, and 20+ severe depression.[14]
Pittsburgh Sleep Quality Index (PSQI)[c]	19 self-rated items and 5 partner-rated items, which measure sleep quality during the previous month. This scale differentiates "good" from "poor" sleepers based on seven areas: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction over the last month.	This scale is the most widely utilized sensitive and specific self-report measure for insomnia. A score above 6 indicates a "poor" sleeper, and a score above 12 is associated with "insomnia."[15]

(continued)

TABLE AI. Continued

Test Name (Abbreviation)	Task Structure	Task Purpose
Combat Exposure Scale (CES)[c]	A 7-item self-report measure that assesses wartime stressors experienced by service members. The total CES score (ranging from 0 to 41) is calculated by using a sum of weighted scores, which can be classified into 1 of 5 categories of combat exposure ranging from "light" to "heavy."	This scale rates cumulative combat exposure and is highly predictive of PTSD, pain and injury, TBI, depression, and other behavioral sequellae.[16]
PTSD Checklist—Military Version (PCL-M)[c]	A 17-item scale assessing symptoms in response to stressful military experiences. This scale assesses PTSD, with subscales including re-experiencing, avoidance/numbing, and hyperarousal.	Higher scores indicate increased PTSD symptomatology. In a military population, scores >49 are likely to have PTSD. For greatest specifically, scores >44 with 3 re-experiencing, 1 avoidance/numbing, and 2 Hyperarousal endorsed as at least "most of the time" are more specific for PTSD and correlate very highly (0.92) with the Clinician Administered PTSD Scale (CAPS).[17]
Deployment Stress Inventory (DSI)[c]	Based upon the neurobehavioral symptom inventory with additional items added to assess anger, pain, and sleepiness. Test is a 28-item experimental scale that factors into three domains (cognitive-emotional, somatic, and anger) and five subscales (cognitive, emotional, pain, sleep, and anger).	This experimental measure is intended to be used as a broad psychological screening tool sensitive to combat-related distress, especially reporting of persistent postconcussive symptoms.[18]

[a]DANA Rapid Battery. [b]DANA Brief Battery. [c]DANA Standard Battery.

sample of nonimpaired service members. The CES correlated mildly with the PCL-m and DSI ($p < 0.01$).

DISCUSSION

The data presented here represent a first empirical examination of the DANA tool, a portable NCAT that includes both cognitive and psychological tests. Feasibility, reliability, and internal validity were assessed through the administration of DANA to 224 active duty service members (officers and enlisted) from the U.S. Air Force, Navy, and Marine Corps across five extreme environments.

As can be seen in Table II, scores were stable across administrations. Split-half reliability correlations for DANA subtests are within acceptable ranges, and are comparable to those reported for other similar NCAT subtests.[9] ICC measures across administrations were excellent and generally exceeded those reported in similar NCAT subtests although they were comparable to previously reported aggregate NCAT scores.[10] We are currently developing more sophisticated scoring and statistical approaches to score each subtest as well as to aggregate subtests into composite index scores.

Descriptive analysis of the psychological subtests shows that the sample scored, in general, well below scores indicative of clinical problems. From the range of CES scores, it appears that most of the sample had not been exposed to moderate or greater combat. With regard to mean psychological scores and the relevant scoring for cognitive variables, all psychological variables correlate highly with each other, with the exception of the Insomnia Severity Index (ISI) and Primary Care (PC)-PTSD, which had moderate correlations, likely due to having a low number of items (4 and 7 items,

TABLE AII. Test Parameters

	No. of Response Trials	Stimulus Presentation Time (milliseconds)	Maximum Response Time (milliseconds)	Intertrial Interval (milliseconds)
SRT	40	900	900	600 to 3,000
PRO	32	2,000	2,000	500 to 1,000
GNG	30	1,500	1,500	1,000 to 1,750
CDS	72	3,000	3,000	900
CDD	72	6,000	6,000	900
SPD	20	5,000	5,000	500 to 1,000
MSP[a]	30	3,000	10,000	750 to 1,350
STN	30	5,000	5,000	900

[a]MSP also had a delay between the stimulus and the response grids of 5,000 milliseconds.

respectively). Similarly, most cognitive tests correlated moderately with each other, with the exception of CDD, which did not correlate with the other cognitive measures, likely tapping into a different construct than the other measures. In addition, in this nonclinical population, no cognitive tests correlated with any psychological tests. This is to be expected given that the great majority of scores on the psychological tests were well within the "normal" range, and the cognitive scores were closely grouped. Finally, CES did not correlate with any measure in this nonclinical population of mostly noncombat deployed service members.

As can be seen in Table III, DANA compares favorably to existing NCATs in terms of median/mean RT (or % accuracy for CDD) and SD. The CVs are also consistent with CVs reported from ANAM data collected in 2006, 2008, and 2012 cohorts. This suggests that differences in absolute values for RT are most likely due to the testing instrument (mouse click versus stylus) rather than anything implicit in the test itself. Taken together, DANA appears to have adequate reliability and test validity in a sample of nonclinical service members across services and environments. DANA is currently being assessed in postdeployment and clinical samples.

The results reported here suggest that the DANA has promise as a next generation NCAT. Benefits of the DANA include that it (a) includes relevant psychological tests as well as standard cognitive tests; (b) is built on a portable OS with more precise timing than previous NCATs; and (c) is a portable handheld device, which is more versatile than a laptop computer. Future studies of DANA are planned to assess DANA's ability to assist frontline providers to more rapidly and accurately evaluate service members to determine the need for higher level evaluation, treatment, or readiness to return to duty.

APPENDIX

Table AI describes the eight cognitive tests and seven psychological questionnaires that were selected for the DANA test batteries. Each individual subtest parameters are shown in Table AII including stimulus presentation duration, response interval, and interstimulus interval.

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AltitudeOmics: The Integrative Physiology of Human Acclimatization to Hypobaric Hypoxia and Its Retention upon Reascent

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Abstract

An understanding of human responses to hypoxia is important for the health of millions of people worldwide who visit, live, or work in the hypoxic environment encountered at high altitudes. In spite of dozens of studies over the last 100 years, the basic mechanisms controlling acclimatization to hypoxia remain largely unknown. The AltitudeOmics project aimed to bridge this gap. Our goals were 1) to describe a phenotype for successful acclimatization and assess its retention and 2) use these findings as a foundation for companion mechanistic studies. Our approach was to characterize acclimatization by measuring changes in arterial oxygenation and hemoglobin concentration [Hb], acute mountain sickness (AMS), cognitive function, and exercise performance in 21 subjects as they acclimatized to 5260 m over 16 days. We then focused on the retention of acclimatization by having subjects reascend to 5260 m after either 7 (n = 14) or 21 (n = 7) days at 1525 m. At 16 days at 5260 m we observed: 1) increases in arterial oxygenation and [Hb] (compared to acute hypoxia: PaO_2 rose 9±4 mmHg to 45±4 while $PaCO_2$ dropped a further 6±3 mmHg to 21±3, and [Hb] rose 1.8±0.7 g/dL to 16±2 g/dL; 2) no AMS; 3) improved cognitive function; and 4) improved exercise performance by 8±8% (all changes $p<0.01$). Upon reascent, we observed retention of arterial oxygenation but not [Hb], protection from AMS, retention of exercise performance, less retention of cognitive function; and noted that some of these effects lasted for 21 days. Taken together, these findings reveal new information about retention of acclimatization, and can be used as a physiological foundation to explore the molecular mechanisms of acclimatization and its retention.

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Competing Interests: CL works for AnthroTronix, the developer of the DANA neurocognitve test, which represents a financial competing interest. This does not alter the authors' adherence to PLOS ONE policies on sharing data and materials.

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Introduction

Millions of people live and work in, or travel to, high altitudes, and many of them are able to adjust successfully to the hypoxic environment of very high altitudes (~5000 m), where ambient oxygen pressure is about half the sea level value. Discovery of the mechanisms responsible for human acclimatization to hypoxia could lead to new ways to improve acclimatization and its retention.

The physiology of how humans respond acutely and adapt to hypoxia has been explored extensively over the last century, yet many questions remain about the attributes that best characterize acclimatization [1]. Most would agree that improving arterial oxygenation and exercise performance are central tenets of

acclimatization, and although no studies have focused on the protection from high-altitude illness that occurs with acclimatization, most would also agree such protection is an important aspect of acclimatization. On the other hand, how cognitive function responds during acclimatization is largely unknown, except from anecdotal reports. Intriguing also are suggestions that acclimatization causes functional modifications that persist upon return to high altitude after weeks, or perhaps even months, at sea level, and at a time when all known physiological measures of acclimatization have returned to normal low altitude values [2–4].

AltitudeOmics is a multifaceted research program on acclimatization to high altitude and the retention of acclimatization after return to low altitude. The goals for AltitudeOmics were 1) to describe a phenotype for successful acclimatization and assess its retention—that is—whether adaptive responses persist after descent to low altitude for one to three weeks, and 2) to use these findings as a foundation for companion mechanistic studies of the human transcriptome, epigenome, metabolome, and proteome (OMICS). Our approach was to study lowland volunteers in the field who were taken rapidly to 5260 m, where they acclimatized for 16 days. They then descended to 1525 m for either seven (n = 14) or 21 (n = 7) days, after which they returned quickly to 5260 m and were retested. This report describes the physiology of acclimatization and its retention for four key features of acclimatization: 1) arterial oxygenation and [Hb]; 2) acute mountain sickness (AMS); 3) cognitive function; and 4) exercise performance. Of particular interest was the acclimatization retention displayed upon returning to 5260 m after even three weeks at low altitude. Subsequent reports will explore changes in OMICS responses and will attempt to link those responses to the physiological phenotype of acclimatization and its retention reported here.

Methods

Ethical Approval and Subject Recruitment

The study was performed according to the Declaration of Helsinki. It was approved by the Institutional Review Boards of the Universities of Colorado and Oregon and by the Human Research Protection Office of the U.S. Department of Defense. The subjects were informed about the possible risks and discomforts of participation in the study before giving their written and verbal consent to participate. Physical examinations and the U.S. Army Physical Fitness Test (APFT) (push-ups, sit-ups, and a 3.2-km run) [5] were performed to characterize health and fitness status. Exclusion criteria included: being born at >1500 m; having traveled to altitudes >1000 m in the past three months (including air travel); using prescription medications; smoking; being pregnant or lactating; having a history of serious head injury (loss of consciousness); self or familial history of migraine; known hematologic or cardiovascular abnormality (e.g., sickle cell trait, cardiac arrhythmia); pulmonary function or diffusion capacity for carbon monoxide <90% of predicted; or failure to meet the minimal age/gender standards for the APFT [5]. Seventy-nine subjects completed the screening. Twenty-four healthy, physically active subjects were enrolled. Two subjects dropped out for non-altitude related medical reasons, and one was never healthy at high altitude due to non-altitude related persistent gastrointestinal illness. Thus, 21 subjects (12 males and nine females, average age 20.8 yrs, range 19–23 yrs) constitute the AltitudeOmics group of subjects included in this and subsequent reports (Table 1).

Timeline. Each subject was studied near sea level (SL) (130 m, average P_B = 749 mmHg, Figure 1), and over three study periods at Mt Chacaltaya, Bolivia; 5260 m; average P_B = 406 mmHg); on the first/second and sixteenth/seventeenth days at 5260 m (ALT1, ALT16), and again upon reascent to 5260 m, after either seven (n = 14) or 21 (n = 7) days at low altitude (POST7 or POST21). Baseline studies at SL, including laboratory (physiologic and OMICS) and field (3.2-km uphill run) tests, were conducted over a two-week period in Eugene, OR, USA. Approximately one month after the SL studies, subjects traveled to Bolivia in pairs on successive days. Upon arrival at El Alto (4050 m) after an overnight flight, subjects immediately descended to Coroico, Bolivia (1525 m; P_B = 639 mmHg). Subjects rested for 48 hrs in Coroico to limit the effects of jet lag and were then driven over three hrs to 5260 m. To provide an acute change in inspired PO_2 from 1525 m to 5260 m, subjects breathed supplemental oxygen (2 L/min, nasal cannula or mask) during the drive. On arrival at 5260 m, the first subject immediately began the experimental protocol described below. The second subject rested while continuing to breathe supplemental oxygen for ~ two hrs until the first subject had completed the arterial/venous catheterization and cognitive testing portion of the protocol. Then the second subject began the protocol as described for the first subject. Two subjects were studied per day for ALT1, ALT16, POST7, and POST21. After completing laboratory testing and AMS scoring on ALT1, subjects slept overnight on supplemental oxygen to minimize the risk of developing severe high-altitude illness. The next morning, subjects completed a 3.2-km uphill run (305 m elevation gain) before descending by car to La Paz, Bolivia (3800 m; average P_B = 487 mmHg) to continue acclimatizing at a lower altitude over three nights (ALT2-ALT4). On ALT4 subjects

Table 1. General Subject Characteristics.

ID	Gender	Age (years)	HT (cm)	WT (kg)	BMI (kg/m^2)
001	M	22	184.2	80.8	23.8
002	M	22	181.6	65.4	19.8
003	F	21	166.4	54.3	19.6
004	M	21	181.6	70.7	21.4
005	F	21	160.0	53.2	20.7
006	M	19	170.2	68.1	23.5
007	M	21	184.2	73.3	21.6
010	F	19	163.8	67.6	25.1
011	F	21	169.5	68.0	23.6
012	M	20	181.6	82.4	24.9
013	M	23	182.9	77.0	23.0
014	M	21	186.7	85.4	24.4
015	F	22	168.3	56.7	20.0
017	F	23	174.0	69.9	23.0
018	M	21	180.3	79.9	24.5
019	F	19	176.5	68.0	21.8
020	F	19	165.7	62.2	22.6
021	M	20	182.9	68.9	20.6
022	M	23	180.3	73.8	22.6
023	M	20	179.1	77.8	24.2
025	F	19	172.1	60.9	20.5
Mean	12M/9F	20.8	175.8	69.7	22.4
SD		1.4	7.9	9.0	1.8

Height (HT); Weight (WT); Body Mass Index (BMI).
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visited 5260 m for four to six hrs. On ALT5, they returned to 5260 m, where they remained for an additional 13 days. On ALT16/17 subjects were tested, as on ALT1/2 prior to descending by car to 1525 m. To test physiological retention of acclimatization after living for seven (n = 14) or 21 (n = 7) days at low altitude (1525 m), subjects returned to 5260 m by car, as they did on ALT1 but this time without supplemental oxygen, and completed the POST7/21 testing (detailed below). After completion of a 3.2-km uphill run on POST7/21, the subjects returned home. Assignment to POST7 or POST21 was determined by each subject based on their desire to stay in the field an extra seven or 21 days. While in Bolivia, subjects were housed and fed as a group. Meals and snacks were kept similar to the subjects' typical *ad libitum* diet. Subjects were instructed to ingest at least three liters of water each day and to remain physically active.

Experimental Protocol. Testing progressed in the following general order: 1) radial artery and antecubital vein catheterization; 2) 30-min supine rest, followed by cognitive function testing; 3) measurement of resting (seated) arterial blood gases and hemoglobin concentration, and blood draw for OMICS samples; 4) cycle ergometry exercise testing; 5) AMS symptom scoring; and, on a separate day, 6) a 3.2-km uphill run. In addition to the studies presented here, within the framework of AltitudeOmics and reported separately, we also assessed cerebral blood flow[6] and cerebral autoregulation [7]; chemical control of breathing [8]; total hemoglobin mass and blood volume compartments; peripherally [9] and centrally [10] derived measures of exercise-induced fatigue; blood flow through intracardiac shunt (patent foramen ovale) and intrapulmonary arteriovenous anastomoses; and OMICS responses (transcriptomics, epigenomics, metabolomics, and proteomics).

Procedures

Anthropometry. Height (cm) was measured at SL only. Body mass (kg) was recorded at SL, ALT1, ALT16, and POST7/21 using the same scale (Seca 770, Hanover, MD, USA), with the subject wearing light underwear and no shoes.

Arterial Blood Gases and Hemoglobin

Under local anesthesia (2% lidocaine) a 20–22 G radial artery catheter (Models RA-04122/RA-04020 Arrow International, Reading, PA, USA) was placed for the duration of experiments conducted at SL, ALT1/16, and POST7/21. Arterial blood samples were drawn anaerobically and immediately analyzed in duplicate for PaO_2, $PaCO_2$, pH (Siemens RAPIDLab 248, Erlangen, Germany), [Hb] and SaO_2 (Radiometer OSM3, Copenhagen, Denmark). Core temperature was measured using an ingestible temperature-sensing pill (CorTemp HQInc, Palmetto, FL, USA)[11,12]. Blood gases were corrected for core temperature [11,12]. CaO_2 (mL/dL) was calculated as: $CaO_2 = 1.39 * [Hb] * (SaO_2/100)+(PaO_2 * 0.003)$. The Hill equation was used to calculate P50 [13]. Resting arterial blood samples were taken following 10 min of seated rest at SL, ALT1, ALT16, and POST7/21.

Acute Mountain Sickness

The severity of AMS symptoms was assessed using the Lake Louise Questionnaire (LLQ), which includes a self-reported assessment of AMS symptoms (headache, fatigue, gastrointestinal discomfort, and dizziness) and the shortened Environmental Symptom Questionnaire (AMS-C). Total LLQ scores that included headache and were ≥3 or ≥6 (out of a possible total of 12) were diagnostic of moderate or severe AMS, respectively. Quality of sleep was not included in the total LLQ score because nights prior to ALT1 and POST7/21 were spent at low altitude. Recently, in our laboratory, we have published LLQ without using the sleep question, with no change in sensitivity in identifying AMS [14,15]. AMS-C is a self-reported 11-question inventory from which a score ≥ 0.7 is considered indicative of AMS [16]. AMS symptoms were assessed at SL, ALT1 (in the evening,

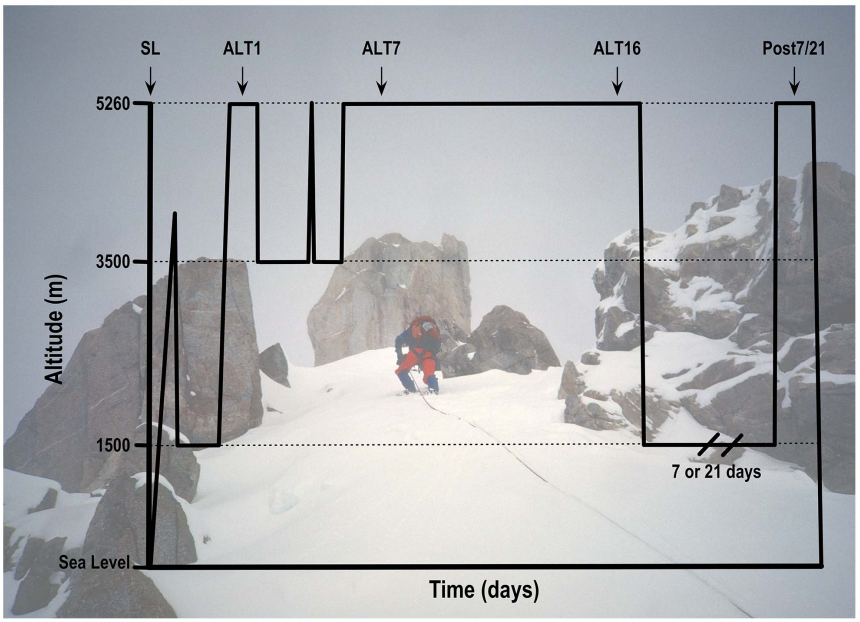

Figure 1. Timeline for AltitudeOmics Studies. Each subject completed this study timeline, with n = 14 staying at low altitude for POST7 and n = 7 staying at low altitude for POST21. Subjects flew from the USA to Bolivia aboard commercial aircraft with no recording of barometric pressure during the flight; the profile for travel in the figure is therefore approximate.
doi:10.1371/journal.pone.0092191.g001

10–12 hrs after arrival), ALT16, and POST7/21 (time-matched to ALT1).

Cognitive Function

The Defense Automated Neurobehavioral Assessment (DANA) was used to assess neurocognitive function. DANA is a neurocognitive assessment tool that includes a library of open-source, standardized, cognitive and psychological assessments [17]. Using a handheld computer, the following nine cognitive function tests were administered: 1) Simple Reaction Time-1 (measured at the beginning of neurocognitive testing to gain an understanding of pure visual-motor response); 2) Simple Reaction Time-2, repeated at the end of neurocognitive testing to assess diminished reserve of cognitive effort on reaction time; 3) Procedural Reaction Time, a measure of choice reaction time and accuracy; 4) Go-No-Go, a measure of speed, accuracy and impulsivity; 5) Code Substitution—Simultaneous, a measure of visual scanning and attention, learning, and immediate recall of digit-symbol pairings; 6) Code Substitution—Delayed Recall, a measure of short-term memory for digit-symbol pairings; 7) Spatial Discrimination, a measure of visuospatial analytic ability; 8) Match to Sample, an assessment of attention and memory for visuospatial discrimination; and 9) Sternberg's Memory Search, a measure of working memory for letters. Neurocognitive tests were administered before and after the expedition at SL and once each at ALT1, ALT16 and POST7/21. Repeat cognitive function tests at SL were similar ($p>0.5$) and thus were combined to give one SL score for comparison to changes in cognitive function at 5260 m. Mean throughput, a measure of mental efficiency, is calculated as the mean number of correct responses for each test made within one min [18] and is the outcome variable reported for all cognitive function variables.

Exercise

Laboratory exercise testing. Incremental exercise tests to maximal exertion on an electrically-braked cycle ergometer (Velotron Elite, Racermate, Seattle, WA, USA) were used to assess peak aerobic power. Subjects completed three-min stages at 70, 100, 130 and 160 Watts, followed by 15 Watts/min increments until they could no longer maintain pedaling at $>$ 50 rpm. Peak aerobic power (Watts) was calculated as: work rate of last stage completed + [(work rate increment) * (time into final stage/duration of stage in seconds)] [19]. Exercise tests were performed at SL, ALT1, and ALT16, but not at POST7/21 due to logistical issues.

Field exercise testing. Subjects completed a timed 3.2-km uphill run as fast as possible, on unpaved roads, with an identical elevation gain of 305 m. Tests were performed at SL at least 48 hrs before the laboratory tests and in the morning after an overnight stay on ALT1, ALT16 and POST7/21. Performance was expressed as mean running speed in m/s.

Data Analysis

As expected, preliminary analyses revealed higher CaO_2 for males as a result of higher [Hb], across the study ($p<0.01$ vs. females); however, since the sex vs. time interaction was not significant ($p>0.05$) male and female data were pooled for all subsequent analyses. For physiological variables, paired t-tests, with Bonferroni correction for multiple testing, were completed for comparisons among time points. LLQ, AMS-C scores and cognitive function tests were evaluated by the Wilcoxon signed rank test. The Spearman rank order and Pearson product moment correlations were run to evaluate associations between changes in arterial blood gases and [Hb] and changes in AMS symptoms, cognitive function, and physical performance across time. Due to transportation delays and the technical challenges inherent to field studies, not all procedures were completed on all subjects at Mt. Chacaltaya (see Tables S1, S2, S3, S4, S5 for respective sample sizes). Overall, most subjects completed most tests, with 88% of arterial blood gas and hematology measurements, 100% completion of AMS and cognitive function tests, and 95% for the 3.2-km uphill run. For all parametric statistical comparisons, $p<0.01$ (Bonferroni correction of 0.05/5) was considered significant, with $p<0.01$ for Wilcoxon signed rank test results considered significant. Individual data for all responses reported here are presented in Tables S1, S2, S3, S4, S5. Data in the text are presented as means $\pm$ standard deviation.

Results

Anthropometry

Height and body mass at SL are presented in Table 1. Body mass was unchanged from SL to ALT1 (p = NS), then dropped by 2.6 ± 1.6 kg ($p<0.01$) from ALT1 to ALT16; it showed no significant change thereafter (Table S1).

Arterial Blood Gases and Hemoglobin

PaO_2, $PaCO_2$, SaO_2, and CaO_2 were reduced with acute exposure to 5260 m (SL to ALT1, $p<0.01$; Figure 2, panels A–C, Table S2), while pH and P50 increased ($p<0.01$, Figure 2, panels D and E) and [Hb] was unchanged (p = NS, Figure 2, panel F). PaO_2, SaO_2, CaO_2, P50, and [Hb] all increased from ALT1 to ALT16, while $PaCO_2$ continued to fall ($p<0.01$, all comparisons) and pH was unchanged (p = NS; Figure 2). SaO_2 at POST7 was maintained at ALT16 levels. In contrast, PaO_2, CaO_2, P50, and [Hb] at POST7 decreased from ALT16 ($p<0.01$) and approached ALT1 values. $PaCO_2$ rose at POST7 from ALT16 values and was significantly different from both ALT1 and ALT16 ($p<0.01$). Since subjects studied at POST21 had incomplete arterial blood gas data at all time points but SL; those data are qualitatively discussed, but data in the text and figures are at all time points for the POST7 group only. The pattern of change from ALT16 to POST21 was similar to that seen from ALT16 to POST7 for PaO_2, $PaCO_2$, SaO_2, CaO_2, pH, and [Hb], suggesting possible retention of acclimatized values for SaO_2, but less so for PaO_2, $PaCO_2$, CaO_2, P50, pH, and [Hb].

Acute Mountain Sickness

LLQ and AMS-C were highly correlated ($R^2 = 0.72$, $p<0.001$) and identified the same subjects as AMS positive at ALT1; for brevity, only the LLQ score is discussed (see Table S3). Eighty-one percent (17/21) of subjects had AMS ($LLQ\geq3$; $p<0.01$ vs. SL) on the evening of their first night at 5260 m; of those with AMS nearly half had severe AMS ($LLQ\geq6$; $p<0.01$vs. SL; Figure 3A). AMS completely resolved in all subjects as acclimatization progressed from ALT1 to ALT16. Upon reascent at POST7 subjects remained free from AMS. On POST21, 3/7 of subjects again developed AMS scores≥3 (p = NS vs. ALT16), but none reported severe AMS. Nobody exhibited HAPE or HACE.

Cognitive Function

Repeat tests at sea level pre-post expedition showed no major differences between individuals or group values ($p>0.5$) and were thus averaged to provide a more robust SL value (Table S4a–c). Five of nine neurocognitive tests showed marked decrements from SL to ALT1 (Simple Reaction Time-1, Simple Reaction Time-2, Code Substitution—Simultaneous, Match to Sample and Procedural Reaction Time, $p<0.01$, Figure 4); no change from SL to ALT1 was seen for Code Substitution—Delayed Recall, Spatial Discrimination, Go-No-Go, and Memory Search ($p>0.05$) (Table

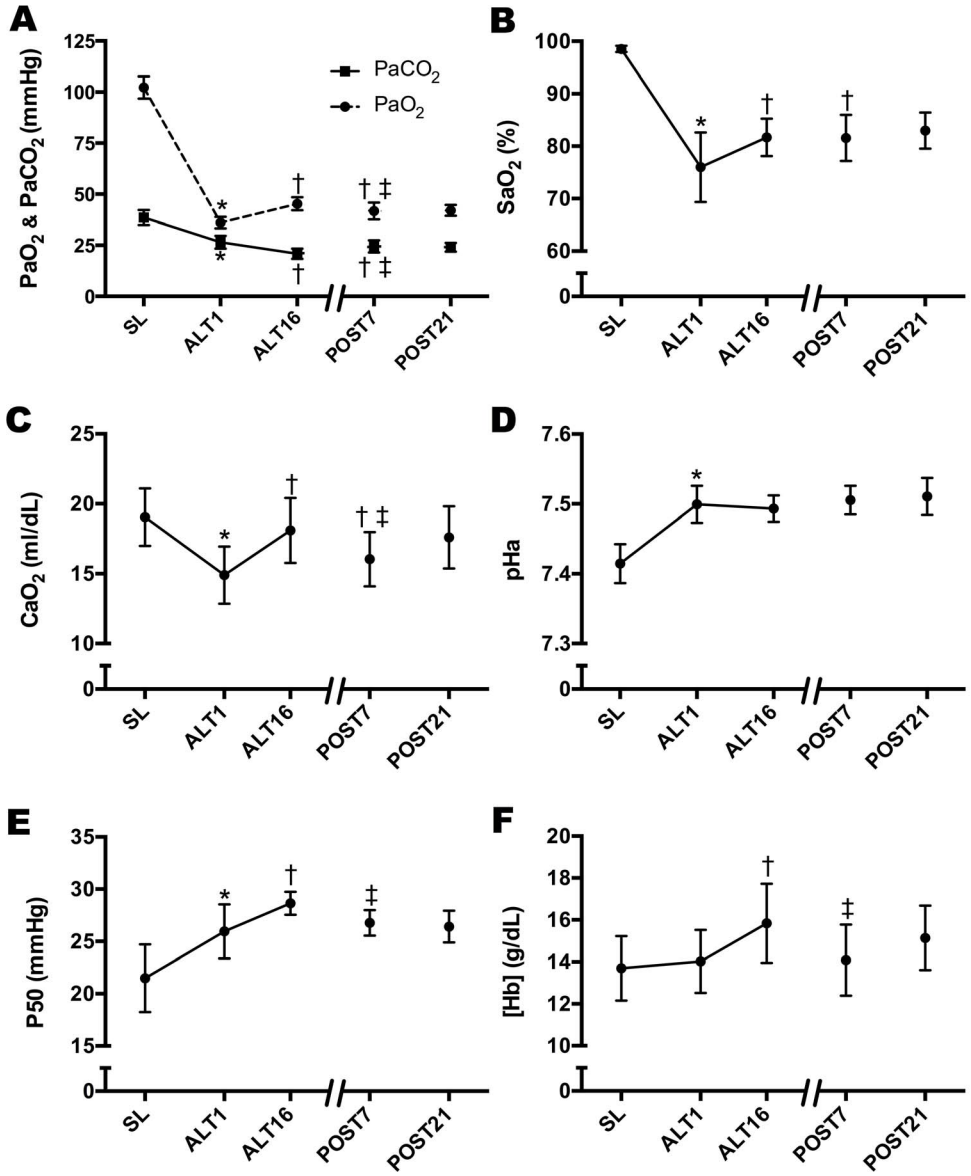

Figure 2. Arterial Blood Gases and [Hb] During Acclimatization and Upon Reascent. Resting indices of ventilatory and hematological acclimatization at SL, ALT1, ALT16, and POST7/21 demonstrating acclimatization after 16 days at a constant altitude and the degree of retention in these variables. *Significantly different vs. SL ($p<0.01$); † significantly different than ALT1 ($p<0.01$); ‡significantly different than ALT16 ($p<0.01$).
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S4a–c). Subsequent analyses focused on the five tests that showed a change with acute hypoxia. Performance improved on Simple Reaction Time-1, Simple Reaction Time-2, Code Substitution—Simultaneous, Match to Sample, and Procedural Reaction Time as acclimatization progressed from ALT1 to ALT16 ($p<0.01$, Figure 4). At POST7, Code Substitution—Simultaneous and Match to Sample showed retention of acclimatization compared to ALT16 ($p<0.01$, Figure 4, panels C and D), with loss of acclimatization evident for Simple Reaction Time-2, Procedural Reaction Time ($p<0.01$, Figure 4, panel B and E), and a trend to loss of acclimatization noted for Simple Reaction Time-1 ($p>0.01<0.05$, Figure 4, panel A). No cognitive function tests showed retention of acclimatization at POST21.

Exercise

Laboratory exercise testing. Peak oxygen uptake at SL was 3.4±0.8 l/min and fell by 29±11% to 2.3±0.6 l/min at ALT1 ($p<0.01$), with no change observed from ALT1 to ALT16 (p = NS) (See Table S5). Peak power output at SL was 265±57 W; it fell by 34±7% to 171±40 W at ALT1 ($p<0.01$), and like peak oxygen uptake, it did not improve with acclimatization. Changes in resting arterial oxygenation and [Hb] from SL to ALT1 to ALT16 were not correlated with peak oxygen uptake (p = NS).

Field exercise testing. Running speed was 44±5% slower at ALT1 compared to SL ($p<0.01$; Figure 5). Running speed improved 8±8% from ALT1 to ALT16 ($p<0.01$) and was maintained at POST7 (p = NS). Subjects maintained acclimatized (ALT16) running speed at POST7 despite 13% lower resting [Hb] and CaO_2. After 21 days at low altitude, running speed tended to be slower than at ALT16 (p = 0.06) and was not significantly different

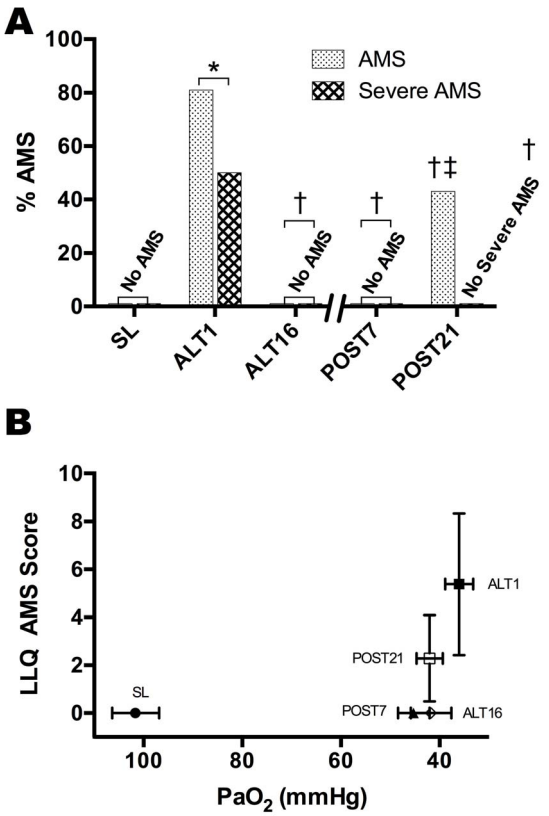

Figure 3. Development of Acute Mountain Sickness, Its Resolution with Acclimatization And Prevention Upon Reascent. Percentage of subjects reporting moderate to severe AMS based on LLQ scores of ≥3, or ≥6, respectively. (A) Symptoms of AMS at ALT1 were alleviated at ALT16 and were largely absent with reascent on POST7/21. (B) Mean PaO_2 and median LL AMS scores reveal no relationship of hypoxemia to AMS. *Significantly different than SL ($p<0.01$); †significantly different than ALT1 ($p<0.01$); ‡significantly different than ALT16 ($p<0.01$).
doi:10.1371/journal.pone.0092191.g003

from ALT1 (p = NS), suggesting a partial loss of acclimatization in running speed by POST21.

Relationship of AMS, Cognitive Function and Exercise Performance to Arterial Oxygenation and [Hb]

During acclimatization AMS, cognitive function, and exercise performance improved, and for AMS and exercise those improvements were retained upon reascent, with only some tests of cognitive function showing retention of acclimatization. The changes that occurred during acclimatization and upon reascent in PaO_2, $PaCO_2$, SaO_2, CaO_2, P50, pH, and [Hb] were not related on an individual (all correlations $r<0.5$) or group basis (all comparisons $p>0.1$) to AMS, cognitive function, or exercise responses. However, the pattern of change with acclimatization in PaO_2, $PaCO_2$, SaO_2, CaO_2, P50, pH and [Hb] matches the pattern of change for AMS, cognitive function, and exercise performance, suggesting an underlying but complex relationship between oxygenation and other aspects of acclimatization.

Discussion

In this paper, we have presented four aspects of altitude acclimatization through a 16-day initial exposure to 5260 m, and upon reascent to the same altitude after either seven or 21 days at low altitude. We found, as have others before us [20–30], elevated arterial oxygenation and [Hb], resolution of symptoms of acute mountain sickness and increased exercise performance after 16 days residence at 5260 m. We also report improvements in measures of cognitive performance that we believe represent a novel and important additional indicator of acclimatization. Most intriguing was finding that after descending to low altitude for one or three weeks, physiological evidence of acclimatization persisted upon returning to 5260 m, as manifest by less AMS, retention of improved exercise performance, and to some extent cognitive performance.

Physiology of Acclimatization

The elevations in arterial oxygenation and [Hb] from ALT1 to ALT16 were similar to those measured in individuals acclimatized for at least 10 days at altitudes ranging from 3800 m to 5260 m [20,26,29,30]. For example, Lundby et al. reported that [Hb] and CaO_2 increased markedly from SL to two weeks at 4100 m, but did not rise further at eight weeks [26]. While similar data do not exist for the rise in PaO_2 and fall in $PaCO_2$ with ventilatory acclimatization at two and eight weeks at a fixed high altitude, Wagner et al. reported after nine weeks at 5260 m a PaO_2 of 50 ± 1 mmHg and a $PaCO_2$ of 21 ± 0.9, values similar to PaO_2 (45 ± 3) and $PaCO_2$ (21 ± 3) in the present study after 16 days at 5260 m [30]. Thus, it seems that≥14 days at 4000 m to 5000 m results in significant acclimatization, and that this duration of exposure can be effective to test acclimatization and its subsequent retention [30].

Sixteen days of acclimatization at 5260 m was effective in reducing the incidence of AMS from 81% in our subjects upon acute exposure to 0% at ALT16, a finding consistent with existing literature [23,24,28]. These findings suggest a new experimental approach to unraveling the pathophysiology of AMS. To our knowledge, no pathophysiological studies of AMS have taken advantage of the complete protection from AMS conferred by acclimatization by comparing individuals upon acute ascent to when they are acclimatized, or upon reascent when presumably the factors that protect from AMS will stand out from other factors that are epiphenomena to the acclimatization process but not key to AMS prevention.

This is the first report of complete recovery of cognitive function to sea level values after acclimatization to high altitude, supporting the idea that cognitive function is an important outcome of acclimatization. DANA tests have negligible practice effects (other than spatial discrimination, which asymptotes after the second administration) [17]. This was evident in the current study, as no significant differences were detected between DANA measures on pre- and post-expedition SL tests. We found that the five tests showing impairment in acute hypoxia all returned to SL values by ALT16 ($p<0.01$, Figure 4). Barcroft et al. reported anecdotal impairment in cognitive function during acclimatization, but lacked any quantitative evidence [31]. Other studies have reported effects on cognitive function in acute hypoxia [32–36] during experiments and expeditions where the barometric pressure and environmental conditions were different at each testing point, such as occurs during a climbing expedition [37–39], and one has speculated about the recovery of cognitive function with acclimatization [40]. However, none of those studies have shown, as in the present study, that when subjects are studied at the same altitude over the course of acclimatization that cognitive function improves to sea level values. DANA tests speed and accuracy in measures that assess attention, simple discrimination, and immediate and incidental memory. Although these measures offer an indication of working memory, they do not assess complex problem-solving and

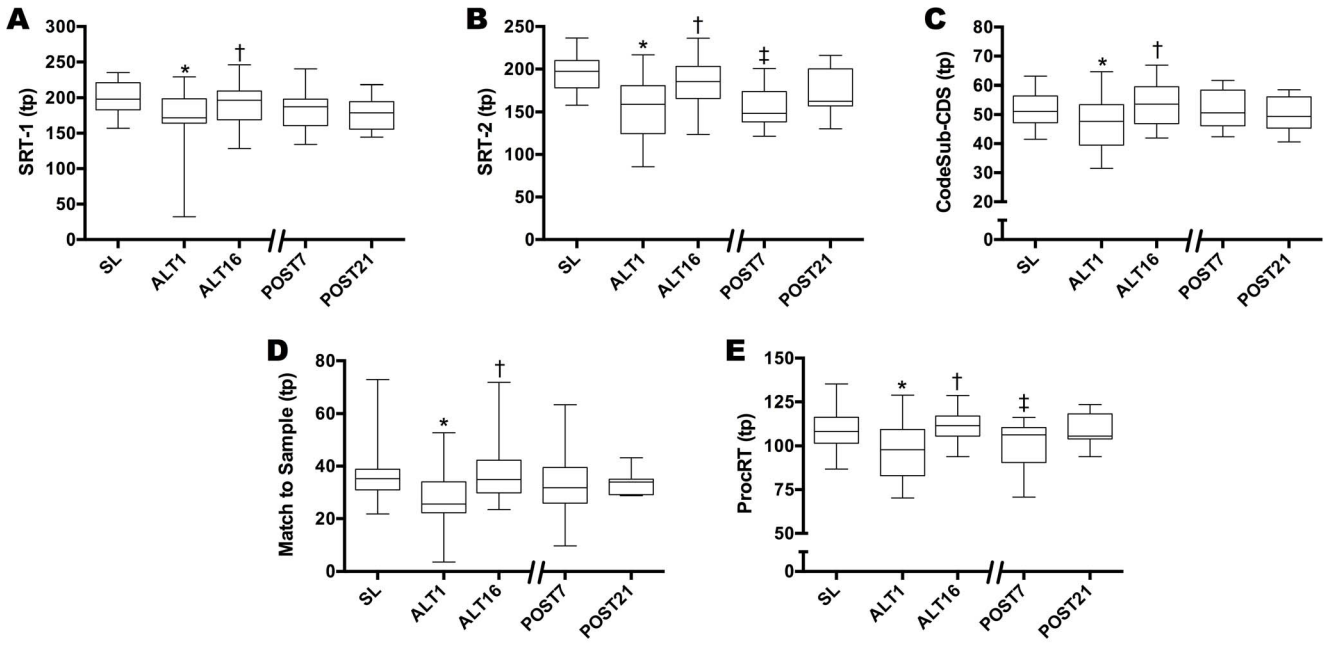

Figure 4. Neurocognitive Function During Acclimatization and Upon Reascent. Five tests of cognitive function revealed marked decrements in performance from SL to ALT1, and improvement back to sea level values by ALT16. Code Substitution—Simultaneous and Match to Sample retained levels found at ALT16 on POST7, while Simple Reaction Time-1, Simple Reaction Time-2, and Procedural Reaction Time essentially reflected a loss of during acclimatization upon reascent at POST7. None of the cognitive function tests showed any retention of acclimatization at POST21. (tp = throughput = mean number of correct responses made within one min). *Significantly different than SL ($p<0.01$); †significantly different vs. ALT1 ($p<0.01$); ‡significantly different vs. ALT16 ($p<0.01$).
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decision-making aspects of executive functioning, which may be especially relevant for people working at high altitudes. Understanding the mechanism for the marked resolution of the initial decrement in cognitive performance that occurs in acute hypoxia has potential impact [41] for anyone visiting, living, or working at high altitudes where impaired cognitive dysfunction is a major challenge [37,38,42].

Our findings for submaximal exercise performance are consistent with other reports showing improvements during acclimatization [22,25,27,43] with no change in peak oxygen consumption [2,22,26,44–51]. However, in retrospect, we question the practical relevance of these all-out efforts, as most work or recreational activities at high altitude are not performed to exhaustion or as fast as possible. For example, mountaineers try to preserve energy to sustain efforts across multiple days and might actually put themselves at risk of serious harm, or death, if they truly reached the point of exhaustion. Their ability to cover more ground faster while preserving a functional reserve is a hallmark of acclimatization supported by anecdotal accounts [52,53]. To the best of our knowledge, only one study before the present report has objectively measured this type of submaximal performance [43]. The physiology behind the improvement in sustained, self-regulated submaximal performance at altitude remains unexplored [2,22,26,43–52].

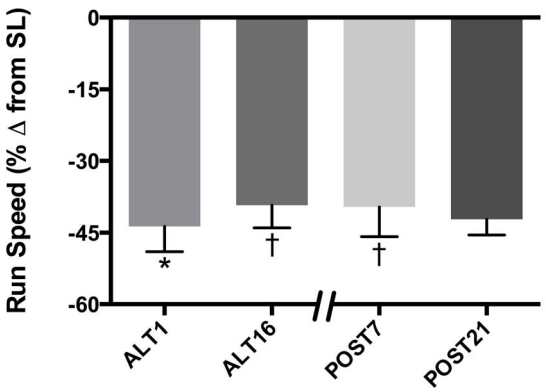

Figure 5. Field Exercise Testing During Acclimatization and Upon Reascent. Uphill running speed plotted as percent change from sea level improved from ALT1 to ALT16 and was retained at POST7, with a trend to retention at POST21. *Significantly different vs. SL ($p<0.01$); †significantly different vs. ALT1 ($p<0.01$).
doi:10.1371/journal.pone.0092191.g005

Physiological Retention of Acclimatization: Arterial Blood Gases and Hemoglobin

At POST7/21, PaO_2 and $PaCO_2$ values ranged between ALT16 and ALT1 values, indicating partial retention of ventilatory acclimatization. In contrast, SaO_2 and pH remained near ALT16 acclimatized levels on POST7/21. We calculated a decreased P50 from ALT16 to POST7/21, suggesting a left shift in the oxyhemoglobin dissociation curve upon reascent as a possible explanation for the retention of acclimatized values for SaO_2 at POST7/21 [2]. These findings are compatible with one previous study showing partial retention of ventilatory acclimatization using noninvasive indices of oxygenation and end tidal CO_2 levels after eight days at low altitude [2,54]. The drop in [Hb] from ALT16 to POST7/21 may be due to selective destruction of the youngest circulating red cells (neocytolysis) upon return to low altitude [55–58], or potentially an increase in plasma volume [59].

Physiological Retention of Acclimatization: Acute Mountain Sickness

Our findings on AMS upon reascent extend the work of others conducted at lower altitudes in demonstrating that previous altitude acclimatization confers some protection from AMS [3,4,60]. The marked efficacy of acclimatization to prevent severe AMS is underscored by comparison to results from clinical trials where acetazolamide only reduced the risk of severe AMS by 44% [61], compared to 100% for acclimatization in our study. Exactly how acclimatization prevents AMS and other high-altitude illnesses upon reascent is unclear.

AMS is clearly triggered by hypoxemia, but once the processes that cause AMS are initiated, the relationship with PaO_2, SaO_2, and CaO_2 is less clear. This is reflected in Figure 3B where AMS scores are highest when PaO_2 is lowest at ALT1, but when at POST7 and ALT16, when PaO_2 levels are only a few mmHg higher than ALT1 values, AMS is absent. Additionally, at POST7, when AMS is absent in all 14 subjects, CaO_2 levels are much lower than at ALT16, suggesting a limited role for CaO_2 in the protection from AMS observed upon reascent. One explanation may be that the absolute value of PaO_2, SaO_2, or CaO_2 is not the critical factor, but rather that acute hypoxia sets in motion the physiological alterations leading to AMS. In other words, perhaps an individual threshold exists that triggers AMS when crossed [62]. Unraveling how this occurs may lead to advances in the understanding of the pathophysiology of high-altitude illnesses.

Physiological Retention of Acclimatization: Cognitive Function

Cognitive function stands out as a key feature of acclimatization to hypoxia that is not completely retained at acclimatized levels upon reascent. The tests that showed retention of acclimatization at POST7 (Code Substitution—Simultaneous and Match to Sample) commonly reflect changes in short-term memory. The tests of reaction time (Simple Reaction Time-1, Simple Reaction Time-2, Procedural Reaction Time) essentially returned to ALT1 values by POST7, indicating a loss of the improvement in reaction time seen with acclimatization. Short-term memory and reaction time appear to represent distinct processes that respond differently to the changes in arterial blood gases and [Hb] from ALT16 to POST7. Understanding the mechanisms responsible for acclimatization retention or its loss could lead to new insights into the links between brain oxygenation and cognitive function for persons at high altitudes.

Physiological Retention of Acclimatization: Exercise

The retention of exercise performance for at least seven days, with partial retention after 21 days spent at low altitude, has important implications for everyone living, visiting, or working at high altitudes. At POST7, and to a lesser extent at POST21, subjects essentially matched their acclimatized running performance. This is the first report of retention of acclimatized exercise performance upon reascent after de-acclimatizing at low altitude. As far as we know, only one other study attempted to measure retention of acclimatized endurance exercise performance [2], but that study showed no improvement in endurance exercise performance with acclimatization, likely due to a small sample size ($n = 6$), thus rendering testing of retention impossible. As noted above, all studies [22,25,27,43] but one [2] have shown improvement in submaximal endurance capacity with acclimatization. The retention of exercise performance shown at POST7 occurred despite significant reductions in resting [Hb] and CaO_2. These findings are contrary to those reporting a direct positive effect of CaO_2 on exercise performance at lower altitudes [25,63], but agree with those reporting little effect of CaO_2 on exercise performance at higher altitudes (>3500 m) [64–66]. If the improvement of exercise performance with acclimatization and its retention upon reascent is not directly related to CaO_2, then other factors must be at play. One possibility is that mechanisms other than oxygen delivery could boost oxygen transport and thus exercise performance during acclimatization and upon reascent, such as elevated circulating blood levels of vasodilatory substances (e.g., nitric oxide [67] or adenosine [68]) or other, as yet unknown, processes. Discovering the mechanisms responsible for improving exercise performance with acclimatization and its retention after acclimatization has potential relevance to exercise tolerance in anyone exposed to hypoxia.

Physiological Mechanisms Explaining Acclimatization and its Retention

Acclimatization transforms a lowlander into someone who is protected from high-altitude illness, has improved cognitive function, and has better exercise performance at 5260 m. In the present study, acclimatization-induced improvements in AMS symptoms, cognitive function and exercise performance appear to follow the time course of ventilatory and hematological acclimatization. But after extensive analysis, no case was found where the degree of improvement in AMS symptoms, cognitive function, and exercise performance was significantly directly correlated to measured indices of arterial oxygenation and [Hb]. Further, arterial oxygenation and [Hb] were poorly correlated with the benefits of acclimatization that persisted upon reascent. Though not well known, Luft et al. reported on the retention of acclimatization based on studies conducted in hypobaric chambers on climbers returning from Nanga Parbat in 1938 [69]. The measurement of retention was tolerance to very high altitudes (>8000 m) measured, in part, by deterioration of handwriting. They noted that neither the hemoglobin concentration nor the erythrocyte count were responsible for the persistence of acclimatization. While we acknowledge the inherent limitations of correlational analyses, the disconnection between ventilatory and hematological acclimatization and physiological function suggests that additional mechanisms are involved in acclimatization and its retention. These might include physiological responses that we did not measure, or molecular and cellular responses in a specific tissue such as brain that cannot be easily measured in humans. In subsequent reports we will pursue a linkage between the OMICS responses and the physiological adjustments described here to explore the mechanisms underlying acclimatization to high altitude and its retention.

Limitations

Several limitations in the study design and execution should be considered. This study was completed in the field, in a foreign country, and with many uncontrolled variables. The rationale for this approach over a trial in a hypobaric environment where many more variables could be controlled was that such a large study could not be completed for a reasonable cost and in a reasonable time-frame in a hypobaric chamber. Operation Everest II studied six-to-eight subjects during a 40-day simulated ascent of Mt Everest. Though many of the time points from Operation Everest II had data from only four to six subjects, many important observations were made from these experiments [29,44,70–73]. But to have sufficient statistical power to combine the OMICS and physiological studies, much larger sample sizes are needed. As far as the authors know, there is one hypobaric chamber in the world large enough to accommodate 21 subjects at a time, located in

Glasgow, Scotland. While we acknowledge the field design as a limitation, we believe this study makes an important contribution to understanding acclimatization that can point to future studies with smaller samples and more focused experimental questions in controlled hypobaric chamber conditions.

This study was limited to 16 days of acclimatization. While this was sufficient time to see marked changes in the variables measured, it is unclear if longer exposure would have resulted in further improvements in acclimatization or better retention of acclimatization upon reascent. Also, due to logistical and financial constraints and to avoid areas of high malarial risk, subjects did not descend all the way to sea level between exposures. However, this may not be a major concern, since our results are consistent with other studies reporting protection from AMS after acclimatization [3,4,60]. Only Lyons et al. [3] reported data from a controlled study of acclimatizing individuals; others used epidemiological observations suggesting AMS protection from acclimatization [4,60]. Also, we made no measurements at low altitude prior to reascent, so a question remains as to how much of the reascent responses were present at low altitude such as hyperventilation, resulting in low $PaCO_2$, versus how much was nascent at low altitude but was rapidly triggered on re-ascent.

An additional concern is that subjects may have de-trained over the 16 days at high altitude, since they were unable to completely maintain their regular exercise regimen. When back at low altitude, subjects resumed their habitual levels of physical activity, potentially restoring some fitness and confounding our measures of exercise performance. Also, changes in total and lean body mass across the study may have affected physical performance [74], but since changes in body composition and training status are inherent to life at high altitude, we feel our results have strong practical relevance.

Finally, the AltitudeOmics project encompasses an extensive suite of physiological and OMICS measurements, and, in its entirety, produced more than 60 million individual data points. Consequently, the data has been partitioned into discrete papers with the ultimate goal of a series of publications that are individually robust and as comprehensive as possible. The physiological parameters included in this paper have historically been used to describe acclimatization, and thus were deemed appropriate as a bridge between past studies and the novel discoveries from AltitudeOmics. Further publications will explore the process of acclimatization by utilizing additional OMICS and physiological data whose inclusion excessively widened the scope of the current paper.

Conclusion

In this study of acclimatization to a very high altitude, we found improvements in key variables after 16 days that describe an acclimatized phenotype by partial acclimatization for arterial oxygenation and [Hb], absence of high-altitude illness, improved cognition and exercise performance. Another intriguing observation is that after descending to low altitude for one or three weeks, evidence of acclimatization persists, as manifested by an acclimatized value for SaO_2, much less severe AMS, maintained exercise performance, and to a lesser extent retention of acclimatized cognitive performance. During the time at low altitude, many of the changes reflecting ventilatory and hematologic adaptation returned to or toward the unacclimatized state at the time reascent measurements were made. In conclusion, this study identifies a phenotype of successful human acclimatization to hypoxia, identifies novel aspects of the retention of the acclimatized phenotype after time at low altitude, and will serve as a foundation for comparing the phenotype of acclimatization with potential mechanistic mediators of acclimatization derived from companion studies of the human transcriptome, epigenome, metabolome, and proteome.

Supporting Information

Table S1 Body Composition. Individual body weight data at SL, ALT1, ALT16, POST7 and POST21 and body fat and lean body mass at SL, ALT1, and ALT16.
(PDF)

Table S2 Resting Arterial Blood Gases and Hemoglobin Concentration. Individual resting arterial blood gases and [Hb] data at SL, ALT1, ALT16, POST7 and POST21.
(PDF)

Table S3 Acute Mountain Sickness Scores for Lake Louise (LLQ) and Environmental Symptom (AMS-C) Questionnaires. Individual AMS symptom scores and the composite LL and AMS-C scores at SL, ALT1, ALT16, POST7 and POST21.
(PDF)

Table S4 a. Cognitive Function Tests. Individual cognitive function test scores for Simple Reaction Time-1, Simple Reaction Time-2, Code Substitution—Simultaneous, and Code Substitution—Delayed Recall at SL, ALT1, ALT16, POST7 and POST21. b. Cognitive Function Tests. Individual cognitive function test scores for Spatial Discrimination, Go-No-Go, Sternberg's Memory Search, and Matching to Sample at SL, ALT1, ALT16, POST7 and POST21. c. Cognitive Function Tests. Individual cognitive function test score for Procedural Reaction Time at SL, ALT1, ALT16, POST7 and POST21.
(PDF)

Table S5 Peak Power Output and Submaximal Exercise Performance. Individual maximal exercise performance and 5-km time to completion data at SL, ALT1, and ALT16 and field exercise testing results at SL, ALT1, ALT16, POST7 and POST21.
(PDF)

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Appendix C

AltitudeOmics: Decreased reaction time after high altitude cognitive testing is a sensitive metric of hypoxic impairment

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Humans experiencing hypoxic conditions exhibit multiple signs of cognitive impairment, and high altitude expeditions may be undermined by abrupt degradation in mental performance. Therefore, the development of psychometric tools to quickly and accurately assess cognitive impairment is of great importance in aiding medical decision-making in the field, particularly in situations where symptoms may not be readily recognized. The present study used the Defense Automated Neurobehavioral Assessment (DANA), a ruggedized and portable neurocognitive assessment tool, to examine cognitive function in healthy human volunteers at sea level, immediately after ascending to an elevation over 5000 m, and following 16 days of acclimatization to this high altitude. The DANA battery begins with a simple reaction time test (SRT1) which is followed by a 20-min series of complex cognitive tests and ends with a second test of simple reaction time (SRT2). Tabulating the performance scores from these two tests allows the calculation of an SRT change score (dSRT = SRT1−SRT2) that reflects the potential effect of mental effort spent during the 20-min testing session. We found that dSRT, but not direct SRT in comparison to sea-level baseline performance, is highly sensitive to acute altitude-related performance deficits and the remission of impairment following successful acclimatization. Our results suggest that dSRT is a potentially useful analytical method to enhance the sensitivity of neurocognitive assessment. *NeuroReport* **25:814–818 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

The partial pressure of oxygen reduces exponentially with increasing altitude and leads to hypoxia, an underlying cause of cognitive and physiological impairment at high altitude. In general, the severity of impairment is a function of both altitude and the rate of ascent, where moderate altitudes (< 2000 m) and slow elevation gains induce little decrement compared with extreme altitudes (> 6000 m) and rapid ascension, which have more severe effects and can result in loss of consciousness or death [1].

Rapid ascent to high altitude results in a number of impairments in cognitive performance (see [2] for review), although it should be noted that fatigue and other travel-related factors must be accounted for before attributing impairment to hypoxia alone [3]. Impairments due to hypoxia have been observed in short-term memory [4], long-term memory and verbal expression [5], attention [6,7], and reaction time [8,9]. Because of the potential impact of these impairments upon high altitude expeditions, the development of field-deployable tools to aid the assessment of hypoxia-induced cognitive impairment is highly relevant to medical decision-making in these scenarios.

In this report, we analyzed an unexamined feature of the neurocognitive data collected from healthy human volunteers on an expedition to Mt Chacaltaya in Bolivia [10]. Cognitive performance was assessed in this study using the Defense Automated Neurobehavioral Assessment (DANA), a software package of public domain cognitive tests that runs on the Android platform. DANA was originally developed as a means of rapidly assessing cognitive changes following mild traumatic brain injury/concussion in deployed service members exposed to blasts, and its reliability has been previously validated in a number of extreme environments [11]. The DANA test battery includes two administrations of a simple reaction time (SRT) task: one at the beginning and one at the end of the ~20-min test session. To investigate the hypothesis that the second measurement of reaction time might reveal an effect of mental fatigue on cognitive performance, we tabulated a dSRT score to compare throughput, a measure of cognitive efficiency, between the two reaction time administrations. Here we show that performance decreases across DANA testing as a function of acute exposure to hypoxic conditions, an

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altitude-related decrement that resolves following successful physiological acclimatization to high altitude.

Methods

Volunteer subjects

As part of the AltitudeOmics study on the physiological signatures of altitude acclimatization [10], DANA was administered to a group of volunteers at sea level (SL) and at 5260 m atop Mt Chacaltaya near La Paz, Bolivia. The study was performed according to the Declaration of Helsinki and was approved by the Institutional Review Boards of the University of Colorado and the University of Oregon, as well as the Human Research Protection Office of the US Department of Defense. The detailed methods for the overall study are summarized here and described elsewhere [10]. Before giving written and verbal consent to participate, each volunteer was informed of the possible risk and discomforts involved in the study. From a pool of 79 volunteers, a total of 24 were recruited under strict criteria including birth at a low elevation (< 1500 m), physical fitness, and general health characteristics (not pregnant or lactating, no prescription drug use, and no history of migraine, loss of consciousness, smoking, cardiovascular abnormality, or pulmonary dysfunction). Of the recruited participants, three dropped out of the study because of medical reasons apart from altitude sickness (e.g. gastrointestinal illness), resulting in a total of 21 participants (12 male, nine female; mean age 20.8 years, range 19–23 years). The constraints of the study, including strict inclusion/exclusion criteria, travel costs, and subject travel availability, produced a small and relatively homogenous sample.

The experiment proceeded according to the following timeline: first, the participants underwent baseline testing at SL (Eugene, Oregon, USA) $\sim$1 month before traveling to Bolivia. After an overnight flight to El Alto (4050 m), the participants immediately descended to Corocio (1525 m) where they rested for 48 h to limit the effects of jet lag. Next, pairs of participants were driven to the top of Mt Chacaltaya (5260 m) over a period of 3 h. During the drive, supplemental oxygen was provided to each participant through either a mask or a nasal cannula (2 l/min) to allow an assessment of acute change upon reaching the destination altitude. After the ascent, one member of each pair immediately began testing, whereas the other continued to breathe supplemental oxygen for 2 h until his/her turn for testing. The assessment was repeated after 16 days of acclimatization at 5260 m, which included descents to La Paz (3800 m) over the first 4 days. A final round of sea-level (SL) testing was conducted $\sim$3 months after returning from Bolivia to collect data from participants who missed the initial SL testing.

DANA administration

The DANA test battery includes the following tests: SRT1, code substitution (simultaneous), procedural reaction time, spatial discrimination, go/no-go, code substitution (delayed), match to sample, and Sternberg memory search. The $\sim$20-min test battery ended with a second administration of simple reaction time (SRT2) according to methodology introduced by Bleiberg *et al.* [12]. The test battery was administered on a Trimble Nomad handheld computer (Android version 2.1; Trimble, Sunnyvale, California, USA). Performance in the tests administered between SRT1 and SRT2 was analyzed elsewhere [10]; for the present purposes, the intervening test battery between the two SRT administrations may be thought of as providing a cognitive challenge to the participant, which we hypothesized to have a negligible effect upon SRT2 under normal conditions.

Each SRT administration consisted of 40 trials with a random intertrial interval (600–3000 ms). Each trial began when a yellow target appeared on a black screen. The participant was instructed to tap the target as soon as it appeared and was asked to perform the task as quickly and accurately as possible. The participants completed four practice trials with feedback before commencing the portion of the test from which data were collected.

Data analysis

Throughput was calculated as follows for each SRT administration per participant:

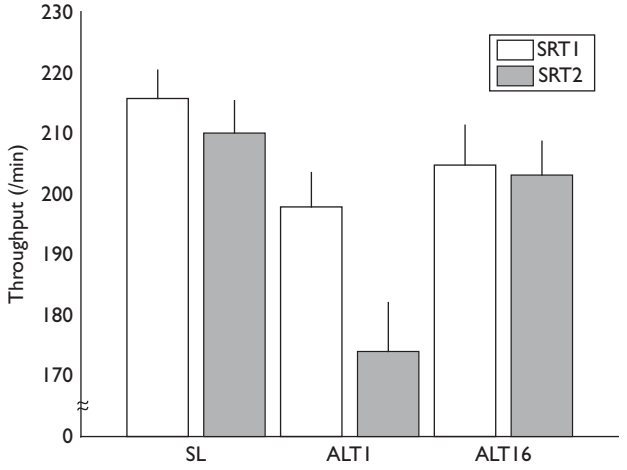
$$\text{Throughput} = \frac{\text{Correct trials (\%)}}{\text{Correct trial median reaction time (ms)}} \times 60000 \left(\frac{\text{ms}}{\text{min}}\right)$$

If the percentage of incorrect trials (i.e. failing to respond within 900 ms or responding in anticipation of the cue) exceeded 33% for any SRT administration, whether because of suboptimal effort, illness, or sleep deprivation, the participant was excluded from the analysis ($n = 2$). A two-way, repeated measures analysis of variance was used to analyze global effects on throughput. Pairwise comparisons were examined using Bonferroni-corrected paired t-tests (significance at $P < 0.05/4 = 0.0125$), and effect sizes were calculated with Cohen's d. Because the average throughput from the two SL administrations was not significantly different (unpaired t-test, $P = 0.51$), the second administration was used for the baseline comparison as it included complete datasets from all of the participants. All analyses were carried out using MATLAB R2013b (Mathworks, Natick, Massachusetts, USA).

Results

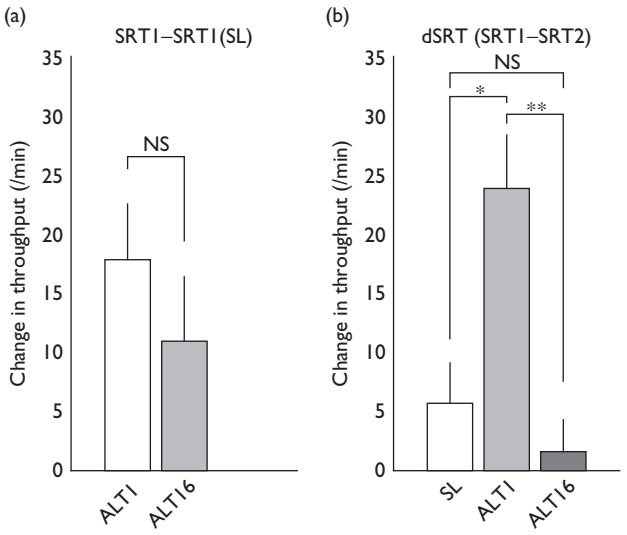
Participant performance in a simple reaction time test was assessed at the beginning (SRT1) and end (SRT2) of a 20-min DANA testing session at SL, following an ascent to 5260 m (ALT1), and after 16 days of acclimatization to this altitude (ALT16; Fig. 1). A two-way, repeated measures analysis of variance with the factors altitude (SL, ALT1, or ALT16) and administration (SRT1 or SRT2) revealed significant main effects of altitude ($F = 15.96$, $P < 0.0001$)

Fig. 1



Throughput in a simple reaction time (SRT) task as a measure of cognitive performance during acute altitude exposure, after acclimatization, and at sea level (SL). SRT was administered before (SRT1) and after (SRT2) cognitive loading with DANA testing. Following acute altitude exposure (ALT1), both SRT1 and SRT2 performance decreased, with a particular decrement in the second administration. Following two weeks of acclimatization (ALT16), performance in the SRT task approximated sea level (SL) scores. Error bars represent SE from the mean. DANA, Defense Automated Neurobehavioral Assessment.

Fig. 2



Quantification of altitude and exertion-related performance changes. (a) Simple reaction time (SRT) performance during acute altitude exposure (ALT1) and following two weeks of acclimatization (ALT16) was compared with sea-level (SL) performance. There was no significant difference between ALT1 and ALT16 when compared with SL throughput. (b) Change in SRT performance across DANA testing was compared for each time point. A marked decrease in throughput was observed at ALT1, whereas ALT16 showed an indistinguishable difference from SL. *$P<0.005$, **$P<0.001$. DANA, Defense Automated Neurobehavioral Assessment.

and administration ($F = 22.02$, $P < 0.0005$), as well as a significant interaction of these terms ($F = 11.37$, $P < 0.0005$) upon SRT throughput.

Post-hoc testing detected no difference between SRT1 and SRT2 throughput at SL ($P = 0.43$). This finding was corroborated by additional analysis of a previously collected dataset [11], in which a similar, ~15-min version of DANA was administered to groups of healthy volunteers in a variety of extreme climates (desert, jungle, aboard a ship, and at high altitude postacclimatization). Paired *t*-tests comparing throughput in SRT1 versus SRT2 failed to reach significance in any of these climates (all P's > 0.05), supporting the conclusion that the intervening tests in the DANA battery do not adversely impact SRT performance in healthy humans under these conditions.

To quantify the apparent altitude-induced impairment in reaction time, we first examined SRT performance by comparing against baseline values, a method favored by many neurocognitive assessment protocols [13,14]. Each participant's SL 'baseline' SRT1 throughput was subtracted from the SRT1 throughput values at ALT1 and ALT16. On average, participants showed a throughput decrease of 17.85 ± 4.71/min (mean ± SE) at ALT1 and 10.97 ± 5.45/min at ALT16 compared with SL baseline. A paired *t*-test revealed that this baseline comparison measure failed to show a significant difference between ALT1 and ALT16 ($P = 0.24$; Fig. 2a).

A second comparison, dSRT, was calculated as the difference in each participant's SRT1 and SRT2 throughput scores at each time point (SL, ALT1, and ALT16). These comparisons revealed that SRT2 throughput decreased at the end of DANA testing by an average of 23.87 ± 4.52/min at ALT1, 1.63 ± 2.71/min at ALT16, and 5.71 ± 3.42/min at SL, showing a significant difference between ALT1 and ALT16 ($P < 0.001$) and between ALT1 and SL ($P < 0.005$; Fig. 2b). In addition, the dSRT comparisons produced much larger effect sizes than the baseline comparison (dSRT ALT1 vs. ALT16 $d = 0.95$, ALT1 vs. SL $d = 0.75$; baseline $d = 0.28$).

Discussion

In accordance with previously collected evidence from healthy human volunteers [11], no difference was detected between SRT1 and SRT2 throughput at SL. These results support the hypothesis that DANA testing does not induce sufficient cognitive loading to alter psychomotor performance in healthy participants under normal inspired oxygen and barometric pressure. However, a comparison of performance in the two SRT administrations unmasked a robust altitude-dependent effect of cognitive exertion upon psychomotor efficiency. The difference score dSRT (SRT1 throughput – SRT2 throughput) shows a significant relationship with acute altitude exposure: a marked decrease in throughput

following cognitive testing emerges after ascent from SL. However, following 16 days of acclimatization to high altitude, throughput scores resemble those seen at SL: SRT1 and SRT2 performances are indistinguishable. These results are in agreement with complementary physiological and cognitive data that were simultaneously collected from the same participants [10]. In contrast, the baseline comparison measure failed to show a significant difference between ALT1 and ALT16. These results indicate that in this context, comparison against baseline was not sensitive to the cognitive effects of acute hypoxia and subsequent acclimatization. Further, the dSRT comparison produced a much larger effect size than the baseline comparison, indicating that dSRT is a robust metric by which cognitive impairment may be quantitatively assessed.

A similar post-testing decrease in reaction time was reported by Bleiberg *et al.* [15] in a study on fatigue in postpolio patients. In this study, an Automated Neuropsychological Assessment Metrics (ANAM) battery [12] was used with a configuration similar to DANA: an SRT task was presented both at the beginning and at the end of a battery of more complex cognitive tests. The participants began the morning with a complete ANAM battery, underwent a 1-h comprehensive functional medical evaluation including motor testing and other fatiguing activities, and then completed a second round of the ANAM battery. Although less than a quarter of the postpolio participants showed a decrement in SRT1, over 50% showed decreased performance in SRT2, a difference which was highly statistically significant. Together with the present results, these data indicate that performance in an SRT task after cognitive loading may be a highly sensitive means for observing cognitive impairment. However, the parameters (e.g. length, difficulty, repetition, etc.) of the testing battery that are responsible for the observed results are yet to be identified. It could be the case that a more condensed assessment may be sufficient to reveal cognitive impairment; alternatively, greater sensitivity to impairment may be achievable using an optimized test battery.

Although the observed decrement in SRT performance upon acute hypoxia exposure could be interpreted as motor fatigue rather than cognitive impairment *per se*, we note that several of the other reaction time tasks interleaved within the test battery did not show a significant difference between SL and ALT1 [10]. Taken together, these results indicate that decreased motor output alone cannot explain the change in performance; however, more research is required to investigate the complex interaction of cognitive and motor processing under these conditions.

Conclusion

Comparing SRT performance at the beginning and end of a DANA test battery provides a more robust and reliable indication of hypoxia-induced cognitive impairment than the typically used comparison against baseline performance. Because SRT throughput does not decrease across testing under normal conditions, these results suggest that calculating the dSRT score is a promising analytical method that may aid neurocognitive assessment in situations where appropriate baseline data are not available.

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Conflicts of interest

Emma B. Roach, Corinna E. Lathan, and Lawrence Wolpert are employed by AnthroTronix Incorporated, developer of the DANA tool.

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Appendix D

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The Impact of Multiple Concussions on Emotional Distress, Post-Concussive Symptoms, and Neurocognitive Functioning in Active Duty United States Marines Independent of Combat Exposure or Emotional Distress

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Abstract

Controversy exists as to whether the lingering effects of concussion on emotional, physical, and cognitive symptoms is because of the effects of brain trauma or purely to emotional factors such as post-traumatic stress disorder or depression. This study examines the independent effects of concussion on persistent symptoms. The Defense Automated Neurobehavioral Assessment, a clinical decision support tool, was used to assess neurobehavioral functioning in 646 United States Marines, all of whom were fit for duty. Marines were assessed for concussion history, post-concussive symptoms, emotional distress, neurocognitive functioning, and deployment history. Results showed that a recent concussion or ever having experienced a concussion was associated with an increase in emotional distress, but not with persistent post-concussive symptoms (PPCS) or neurocognitive functioning. Having had multiple lifetime concussions, however, was associated with greater emotional distress, PPCS, and reduced neurocognitive functioning that needs attention and rapid discrimination, but not for memory-based tasks. These results are independent of deployment history, combat exposure, and symptoms of post-traumatic stress disorder and depression. Results supported earlier findings that a previous concussion is not generally associated with post-concussive symptoms independent of covariates. In contrast with other studies that failed to find a unique contribution for concussion to PPCS, however, evidence of recent and multiple concussion was seen across a range of emotional distress, post-concussive symptoms, and neurocognitive functioning in this study population. Results are discussed in terms of implications for assessing concussion on return from combat.

Key words: adult brain injury; behavioral assessments; cognitive function; head trauma; military injury

Introduction

Approximately 1.5 million Americans survive a traumatic brain injury (TBI) from traffic accidents, assaults, sports, and work injuries, with the vast majority of these being primarily mild (mTBI), otherwise known as concussion.[1] Concussion, however, is uniquely problematic in the military given the new strategies of war encountered by service members when fighting an insurgency using improvised explosive devices. The rate of concussion experienced by United States (U.S.) service members engaging in combat during the wars in Afghanistan and Iraq has been estimated at between 15% and 22%.[2–4]

Concussion can affect cognitive, somatic, and emotional functioning, including slowed and less accurate information processing, sensory sensitivity, imbalance, headaches, and emotional lability.[5] Although most symptoms of concussion appear to dissipate within hours or days, lingering effects of concussion have been widely reported,[6–8] with persistent post-concussive symptoms (PPCS) reported in between 15% and 50% of persons with mTBI, depending on how it is defined and assessed.[5] Several studies show that at least a subgroup of persons do continue to have both subjective symptoms,[9–13] physical symptoms,[14] and lower cognitive test performance, even after 90 days.[15,16]

It has been argued, however, that the rates of PPCS are actually much lower or that any lingering symptoms are not from concussion at all, with any persistent effects on cognitive and somatic functioning exclusively because of the presence of concomitant emotional problems such as post-traumatic stress disorder (PTSD) and depression.[2,17–21] Indeed, the extent to which the effects of concussion persist has been a topic of intense debate with substantial

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clinical and policy implications, including recommendations that the military halt post-deployment assessment of post-concussive difficulties, focusing instead on emotional difficulties associated with cognitive and somatic complaints.[22]

The discrepancies between reports of PPCS in the literature may arise from several factors. First, the populations investigated may vary. Rates and symptom manifestations of PPCS across studies may be because of differential levels of emotional comorbidity in patients who were concussed from sports injury compared with accident, assault, or combat. Findings may also vary based on whether the sample studied was assessed in a clinical setting, leading to the possibility of exaggeration of self-reported symptoms because of secondary gain, compared with an anonymous sample outside a clinic setting.

Second, the influence of number and recency of concussions may not have been adequately assessed. Most studies compare the presence of a previous or recent concussion versus no concussion. The number of lifetime concussions, however, has not been adequately evaluated. A few recent studies have begun to show an association of multiple concussions with persistent neurocognitive and emotional symptoms. This is seen in long-term follow-up studies of professional contact sports[23–25] as well as among active duty personnel.[26] For instance, Bryan and Clemens[27] recently found an association between lifetime number of concussions and suicidal ideation in a small sample of recently concussed military personnel, independent of the effects of depression and PTSD, yet whether these symptoms persisted weeks after the injury was not assessed.

Thirdly, the degree of co-occurring emotional, somatic, and cognitive disorders may cloud the assessment of the individual contributions of these factors to overall functioning, requiring sufficient assessment of these components along with analytic methods to tease apart their individual effects.[28] Because there is a large overlap in post-concussive symptoms with symptoms common in patents with depression and PTSD,[29–31] it is difficult to distinguish among these unless assessments of both concussion and emotional distress are administered together. It is additionally complex to assess the unique contribution of concussion to functioning in combat veterans because of the stress of combat during which service members are dealing with the ever present threat of death, being away from loved ones, and the stress of deployment. Indeed, Cooper and associates[17] found that deployment stress was associated with PPCS, and Vesterling and colleagues[32] found cognitive functioning declining across the deployment cycle, independent of concussion.

It is because of such an association between emotional distress commonly seen in combat and post-concussive complaints that many argue that post-concussive complaints are the direct result of emotional distress alone. It has also been argued, however, that concussion lowers the threshold for developing emotional problems.[33] Morrisette and coworkers[34] found evidence suggesting that recently deployed service members' concussions led to higher rates of depression and PTSD after deployment; Maguen and colleagues[35] found an association between multiple concussions and rates of PTSD 2 years later in combat veterans; and Bryan[26] found an association between number of concussions and sleep difficulty in deployed service members. Despite the many comorbid conditions that exist in military members who have been concussed, distinguishing the unique contributions of concussion from the effects of emotional distress is not always considered when studying the causes of PPCS.

Finally, few studies examining PPCS have assessed both objective measures of functioning, such as cognitive performance, along with subjective self-report of emotional and somatic functioning. It is well known that cognitive functioning can be impaired for at least the first few days after concussion.[5,36] Speed and accuracy (and their combined measure of mental efficiency, throughput [TP]) have been shown to decline across a range of cognitive functions, including simple reaction time[37] as well as delayed memory and executive functioning.[15] Although this problem has been discussed for decades, few studies have examined the long-term effects of concussion on post-concussive neurocognitive functioning and corresponding subjective reports of cognitive, sensory, somatic, and emotional symptoms.[38] The interpretation of cognitive dysfunction after concussion is complicated, because it is also known that emotional distress affects cognitive functioning. This may be even more complicated in combat veterans, because several studies have also shown that cognitive performance is affected by the stress of having been combat deployed.[32,39,40]

In light of the above discussion, there is little consensus as to the nature of persistent post-concussive symptoms in those with a previous concussion. Therefore, the aim of this study was to determine whether the recency and number of lifetime concussions had a sustained impact on emotional, somatic, and cognitive functioning in a sample of U.S. Marines, independent of deployment stress, and symptoms of depression and PTSD. A cohort of U.S. Marines was thought to be ideal for this examination because of the uniformity of the sample, the high rates of exposure to blast, the high rates of co-occurring PTSD and depression, and the high level of functioning compared with a patient population, allowing for an examination of the effects of concussion recency and number on cognitive and somatic functioning, relatively independent of self-report emotional difficulties or exaggeration of symptom because of secondary gain compared with a clinic sample. In addition, Marines from the same unit who had not been deployed or who had been previously (but not recently) deployed allowed for an analysis of the independent effects of deployment stress. Determining the separable effects of these factors will aid in the debate over whether assessment and treatment of concussion should continue in the military.

Methods

Participants

U.S. Marines ($n = 646$) from the Second Expeditionary Force (2MEF) participated in the single testing session reported here. Volunteer participants were all active duty service members in good standing (not on limited duty medical status or pending medical or disciplinary discharge). Testing took place in 2012 at Marine Base Camp Lejeune, where an entire neurobehavioral battery was administered, and at Marine Corp Air Grand Combat Center, Twentynine Palms, where the entire neurobehavioral battery was administered to some participants, but because of time constraints, only a portion of the neurobehavioral battery was administered to others (see list of measures). Marines were recruited for participation independent of their medical or deployment history.

Procedure

Medical officers arranged for 2 hours of time off from duties for service members who might be interested in participating in this study, informing them that researchers were developing an instrument that might eventually be used to improve medical problems in the field. Service members showed up at an appointed time in a classroom to hear a briefing about the research. After an explanation of the procedure that took place without the presence of

commanding officers or senior enlisted personnel in their chain of command, volunteers were allowed to leave or sign the Department of Defense Institutional Review Board approved consent to participate. No remuneration was offered, and care was taken to insure that participation was voluntary, without recrimination for refusing to participate or leaving during testing. No identifiable information was collected, other than age, rank, and sex. There was greater than a 99% agreement to participate from those who came to hear the briefing.

Groups of approximately 20–40 consented service members were administered neurocognitive and self-report and psychological measures on a handheld computing device, in classrooms at either Marine Base Camp Lejeune or Marine Desert Warfare Training Center, Twentynine Palms. The full (Standard) testing battery reported here took approximately 40 min to complete, with the subset (Rapid or Brief) battery taking approximately 10 min (see list of measures). After an explanation of the procedure, handheld devices were distributed. For the neurocognitive tests, participants were instructed to answer as rapidly and accurately as possible. All tests were self-explanatory, beginning with written instructions. After completion of the test battery, service members were administered additional testing for determining reliability. Only the first test administrations are discussed here, because reliability of this instrument has been reported elsewhere.[41]

Materials

Testing materials was administered on a handheld computing device, programmed with the Defense Automated Neurobehavioral Assessment software (DANA). DANA combines a traditional Neuro Cognitive Assessment Tool (NCAT) with other behavioral assessments. All subjects were administered the DANA Standard battery consisting of eight different neurocognitive tests assessing speed and accuracy across a range of simple motor and visual discrimination to more complex memory and decision-making tasks, as well as five self-report psychological assessments. Subjects used a Trimble NOMAD handheld computing device and were instructed to use a stylus for consistency. The NOMAD uses the Android Operating System and has a 3.5-inch color pressure sensitive touch screen. This format is optimally suited for tests of speed and accuracy because it has less variability than can be achieved across various desktop computers.

DANA was funded by and developed for the Department of Defense for use by medical support personnel in the field to detect impaired performance because of deployment-related factors including concussion, emotional distress, or exhaustion. Although DANA uses standard assessments tools that have been well researched and widely utilized, because of its unique delivery system, DANA was tested under extreme field conditions as well as classroom settings, and found to have adequate test-retest (>0.70) and split-half (>0.80) reliability[41] and cross-platform validity compared with the Automated Neuropsychological Assessment Metric (ANAM), the standard neurocognitive assessment used by the military.[42]Neurocognitive tests in the DANA Standard Battery used to assess speed and accuracy included Simple Reaction Time (SRT1), Procedural Reaction Time (PRT), Go-No-Go (GNG), Spatial Rotation Discrimination (SPD), Code Substitution Simultaneous (CDS), Code Substitution Recall (CDR), Sternberg Memory Test (STN), and a second Simple Reaction Time (SRT2).

Depending on the test, between 20 and 40 trials per test are administered, and average speed, accuracy, and TP are calculated for each of these tests. The Standard Battery also included five self-report psychological tests: Post-Traumatic Symptom Disorder Check List, military version (PCL-M), Primary Care Health Questionnaire depression module, minus the suicide question (PHQ-8); Pittsburgh Sleep Quality Inventory (PSQI), the Deployment Stress Inventory (DSI), a modification of the Neurobehavioral Symptom Inventory adapted for deployed service members that includes questions about anger and distress, and the Combat Exposure Survey (CES). For each behavioral assessment, total score was calculated. Accepted clinical threshold scores were calculated for dichotomous analyses. Demographic and concussion history was also included in the battery.

Neurocognitive measures. Data Cleaning was conducted for neurocognitive tests. Responses that are considered too fast (faster than 150 msec for SRT and 250 for other measures) and lapses (slower than 850 msec for SRT or timed-out for the response time for other tests, approximately 2000 msec) are considered incorrect responses and not calculated in mean, Standard deviation (SD), percent correct, or TP scores. Neurocognitive tests that have less than 66% correct responses are considered invalid. Valid summary test scores were calculated to determine mean correct (Mean), SD, percent correct (% correct), and TP (mean correct responses divided by total trials within 1 min), a test of cognitive efficiency. Descriptions of all assessment measures are listed below.

SRT.[a,b,c]. The subject taps on the location of the yellow asterisk symbol as quickly as possible each time it appears. This task measures pure reaction time.

PRT.[a,b,c]. The screen displays one of four numbers for 3 sec. The subject presses on a left button (''2'' or ''3'') or right button (''3'' or ''4'') depending on the number pressed. A choice reaction time measure of accuracy, reaction time, and impulsivity. This choice reaction time task targets simple executive functioning with easy decision-making capabilities.

GNG.[a,b,c]. This is a forced choice reaction-time task relevant to warfighters. A house is presented on the screen with several windows. Either a ''friend'' (green) or ''foe'' (white) appears in a window. The respondent must push a ''fire'' button only when a ''foe'' appears. A choice reaction time measure of sustained attention and impulsivity. The test assesses speed and accuracy of targets, omissions, and commissions.

SPD.[b,c]. Pairs of four-bar histograms are displayed on the screen simultaneously, and the subject is requested to determine whether they are identical. One histogram is always rotated either ± 90 degrees with respect to the other histogram. Assesses visuospatial analytic ability.

CDS.[c]. Subjects refer to a code set of nine symbol-digit pairs that are shown across the upper portion of the screen. A sequence of single symbol-digit pairs is shown below the key, and the subject indicates whether or not the single pair matches the code by pressing Yes or No. Assesses visual scanning and attention, learning, and immediate recall.

Code Substitution–Delayed Memory[b,c] *(CDD).* After a delay of several intervening tests, the same symbol-digit pairs are presented without the code. The subject indicates whether or not the pairing was included in the code that was presented in the earlier Code Substitution learning section. Assesses learning and short-term memory.

[a]DANA Rapid Battery.
[b]DANA Brief Battery.
[c]DANA Standard Battery.

STN.[c]. The subject memorizes a set of five letters, after which letters appear on the screen one at a time, and the subject determines if the letter on the screen is a member of the memory set. Assesses working memory.

Self-report measures. Self-report psychological questionnaires were programmed in DANA and administered on the handheld device after the neurocognitive assessments. One question appeared at a time. Wording was unchanged from the original questionnaires. Service members were instructed to answer as accurately as possible, but that they could skip a question if it disturbed them.

PCL-M.[c]. A 17-item scale assessing symptoms in response to stressful military experiences. This scale assesses PTSD, with subscales including Re-Experiencing, Avoidance/Numbing, and Hyperarousal. Higher scores indicate increased PTSD symptomatology. In a military population, scores >50 are in persons likely to have PTSD. For greatest specifically, scores >44 with three Re-Experiencing, one Avoidance/Numbing, and two Hyperarousal endorsed as at least ''most of the time'' are more specific for PTSD and correlate very highly (0.92) with the Clinician Administered PTSD Scale (CAPS).[43]

Primary Care PTSD Screen[b] *(PC-PTSD).* Four screening questions designed for use in clinical settings to screen for PTSD, with three of four endorsed items suggestive of likely PTSD. Questions assess Hyperarousal, Re-Experiencing, and Avoidance for PTSD Screening. This test is more sensitive than specific, but correlates highly with the PCL.[44,45]

PHQ8. An eight-item Depression Scale assessing symptom severity and diagnostic criteria for major depressive disorder. For research purposes, item #9 (concerning suicide) was not included, yet previously published results indicate that the scoring, reliability, and clinical validity are similar.[46] A person with a score of 0–9 is likely to have no depression, 10–14 mild depression, 15–19 moderate depression, and 20+ severe depression.

CES.[c]. A seven-item self-report measure that assesses wartime stressors experienced by service members. The total CES score (ranging 0 to 41) is calculated by using a sum of weighted scores, which can be classified into one of five categories of combat exposure ranging from ''light'' to ''heavy.'' This scale rates cumulative combat exposure and is highly predictive of PTSD, pain and injury, TBI, depression, and other behavioral sequellae.[47]

DSI. The DSI is an adaptation of the Neurobehavioral Symptom Inventory–22 (NSI), with six additional questions assessing anger and distress adapted for a deployment context. Consistent with others,[48] factor analysis revealed factors referred to as post-concussive symptom subscales in the current analysis: Neurocognitive (worsening focus, concentration, memory), Sensory (alterations in sensitivity to light, sound, smell), Somatic (increased pain, sleep, discomfort), and Vestibular (difficulties with balance or feeling dizzy), as well as total score. Because emotional complaints are better assessed through other measures included in the battery, they are not included in the current analysis of the DSI.

Insomnia Screening Index[b] *(ISI).* A five-item scale evaluating perceived insomnia severity and sleep habits. Each item is rated on a five-point scale (0–4). The total score ranges 0 to 28, and higher scores indicate more severe insomnia. A cutoff score of 10 has been shown to indicate insomnia.[49]

Pittsburgh Sleep Quality Index[c] *(PSQI).* Nineteen self-rated items and 5 partner-rated items, which measure sleep quality during the previous month. This scale differentiates ''good'' from ''poor'' sleepers based on seven areas: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction over the last month. This scale is the most widely used sensitive and specific self-report measure for insomnia. A score above 6 indicates a ''poor'' sleeper.[50]

Demographics and background questionnaire. Service members were asked about age, gender, rank, deployment history.

Concussion questions. Based on the Post-deployment Health Assessment used for all deployed personnel, service members were asked about their history of concussion, including number of lifetime concussions, when their most recent concussion occurred, the immediate effects of the concussion on their cognitive status (dazed and confused, loss of memory, loss of consciousness), and current post-concussive symptoms.

Hypotheses

The relationship of recency and number of lifetime concussions on emotional distress, post-concussive symptoms, and neurocognitive functioning was examined. It was predicted that recency of last concussion and number of lifetime concussion would be negatively associated with emotional distress, post-concussive symptoms, and neurocognitive functioning, and further that concussion uniquely contributes to these factors independent of PTSD (PCL-M) or depression (PHQ-8) scores or deployment factors (time since deployment, CES).

Planned analyses

IBM SPSS v20.0 was used to calculate power and conduct all analyses. Sample size was initially determined from a power estimate of the differences between two groups (concussed – not concussed) to find at least a small effect size in SRT or PCL, based on the expected presence of at least 15% reported concussion, 15% PCL-M scores >50, and 15% PHQ >10 in those recently returned from a recent combat deployment. Power was also calculated based on stability of measures and expected standard errors determined in the Phase 1 pilot study.[41]

Descriptive reporting includes mean correct responses (Mean), SD, percent correct (%Correct), and TP for all neurocognitive scores; mean and SD for self-report psychological scores, and mean or number of cases and SD for age, sex, and number and recency of concussions. TP was used for analyses of interest for all cognitive tests, except for GNG and CDD where %Correct is the metric of relevance.

The effects of recency of concussion and number of lifetime concussions on neurocognitive, emotional, and post-concussive scores are examined first with a univariate General Linear Model on continuous variables. Generalized Linear Modeling (with Wald statistic and Robust Estimator) was used to confirm significance when groups were associated with unequal variances per the Levine test of homogeneity. Pairwise comparisons between type of deployment and number of concussions using the Bonferroni correction were used to adjust for type-I error. PTSD (PCL-M), depression (PHQ-8), deployment history (never, recently within 6 months, and previously—longer than 6 months ago), and combat exposure (CES) scores were used as covariates to determine the unique contribution of concussion to emotional, post-concussive, and neurocognitive measures. PCL-M and PHQ-8 scores were not used as covariates when they were the outcome under investigation.

Logistic Regression was used to determine the odds ratios (OR) for the contribution of concussion to clinical cutoff scores for emotional measures (PCL-M >49; PHQ-8 >10; DSI-Anger >1 SD), and for neurocognitive functioning scores more than one SD

from the mean. PCL-M, PHQ-8, deployment history, and CES covariates are included in these analyses as well unless the covariate is the outcome measure of interest (PCL-M, PHQ-8). Effect sizes are reported as partial eta^2 (η^2_p) for analysis of variance and ORs for Logistic Regression. Description of effect sizes as small, medium, and large is based on the Cohen interpretation.[51] Because this is a single period analysis, data will be analyzed for the exact number of subjects who took the tests in the analysis without extrapolating for missing data.

Results

The total sample size consisted of 646 U.S. Marines with an average age of 22.7 years (SD = 2.7), including 18 females. Because the chain of command was asked not to be present, almost all service members were junior enlisted (E2–E4). There were 234 service members who had never been deployed, 98 who were previously deployed (more than 1 year before assessment) and 314, all men, who were recently deployed (returning from combat deployment in Afghanistan within 3–6 months of testing). Of the 646 service members who were administered the assessment tool, 369 received the Standard Battery and 227 were administered the Rapid or Brief Battery. Because the Rapid and Brief Batteries are contained within the Standard Battery, calculations are based on $n = 419$ involving measures of PCL-M, PSQI, DSI, SPD, CDS, CDD, and STN, and 646 for all other measures (CES, PHQ-8, SRT, PRT, GNG).

Of the entire sample, 25%reported having been previously concussed at some point in their lifetime at least once, 7% reported two previous concussions, and 9% reported three or more times. Deployment status (never, previous, recent) and CES scores were associated with number and recency of concussions, PCL-M, PHQ-8; DSI-Anger, DSI-Total, PSQI, and the majority of the neurocognitive tests with moderate to large effect sizes. Therefore, deployment status and CES were included as covariates in all analyses. PCL-M and PHQ-8 are also included whenever they were not the outcome variables of interest.

Effects of concussion on emotional symptoms

Despite including covariates, having ever had one or more concussions was associated with PCL-M scores ($F = 15.55$, $p < 0.000$, $\eta^2_p = 0.034$), PHQ-8 scores ($F = 5.38$, $p < 0.021$, $\eta^2_p = 0.021$), and DSI-Anger ($F = 9.67$, $p < 0.002$, $\eta^2_p = 0.023$) compared with never having received a concussion. This was likely because of the presence of multiple concussions, however, because having had only one concussion was not associated with emotional distress greater than having no concussions. Recency of concussion was significant for PCL-M scores ($F = 9.93$, $p < 0.000$, $\eta^2_p = 0.046$); PHQ-8 scores ($F = 6.67$, $p < 0.001$, $\eta^2_p = 0.031$); and DSI-Anger ($F = 10.0$, $p < 0.000$; $\eta^2_p = 0.055$). Multiple concussions was significant for PCL-M ($F = 7.62$, $p < .0000$, $\eta^2_p = 0.053$), PHQ-8 ($F = 4.54$, $p < 0.004$, $\eta^2_p = 0.032$), and DSI-Anger ($F = 5.79$, $p < 0.001$, $\eta^2_p = 0.041$).

Bonferoni corrected pairwise comparisons showed that a recent concussion was associated with more distress than distant concussion, and three or more lifetime concussions were associated with more distress than none or one concussion (at least $p < 0.05$ in all cases). Two lifetime concussions were not significantly different from zero or one, or from three concussions.

No interaction between recency and number of concussions was found for either PHQ-8, PCL-M, or DSI-Anger, although those who reported having three or more lifetime concussions with the most recent within the past 6 months averaged a notably higher score (PHQ = 11; PCL = 44; DSI-Anger = 5.5) compared with those without a history of concussion (PHQ = 5; PCL = 31; DSI-Anger = 1.5). The lack of statistical significance for these analyses was likely because of low sample sizes for those who were recently concussed and had multiple concussions; power was far too low to detect a significant difference (observed power was between 0.10 to 0.16).

Binary Logistic Regression with forward stepwise Wald model to eliminate shared variance and including covariates was significant for three versus zero or one lifetime concussions predicting PCL > 50 (Wald = 22.11, $p < 0.000$, OR = 2.48, confidence interval [CI]: 1.70–3.63); PHQ > 10 (Wald = 4.88, $p < 0.027$, OR = 2.19, CI: 1.09–4.40), and DSI-Anger > 1 SD (Wald = 10.15, $p < 0.001$, OR = 4.36, CI: 1.76–10.80).

Thus, the presence of at least one earlier concussion, independent of deployment and CES, was associated with emotional distress, with small effect sizes (Table 1). Multiple and recent concussions, independent of covariates, were associated with emotional distress with stronger effect sizes, and three or more lifetime concussions more than doubled the odds of reaching clinical cutoff scores for PTSD and depression, and had four times the odds of anger problems.

Effects of concussion on post-concussive symptoms

To explore the relationship of concussion to reporting of persistent post-concussive symptoms, continuous variables of the DSI subscales and sleep issues from the PSQI were analyzed incorporating covariates of previous deployment, CES, PCL-M, and PHQ-8. The presence of at least one previous concussion was not related to DSI-Cognitive symptoms, DSI-Sensory symptoms, DSI-Vestibular, or DSI-Total, but was associated with DSI-Somatic symptoms with a very small effect size ($F = 5.67$, $p < 0.018$, $\eta^2_p = 0.014$), and with sleep problems on the PSQI ($F = 13.93$, $p < 0.000$, $\eta^2_p = 0.038$). Planned comparisons of number of concussions using the Bonferroni correction, however, showed that DSI-Somatic and insomnia findings were likely because of the presence of multiple concussions, because only one previous concussion did not significantly vary from no history of concussions.

Recency of concussion was associated with DSI-Sensory ($F = 5.56$, $p < 0.004$, $\eta^2_p = 0.026$), DSI-Somatic ($F = 5.00$, $p < 0.002$, $\eta^2_p = 0.024$), DSI-Vestibular ($F = 6.45$, $p < 0.002$, $\eta^2_p = 0.030$), and PSQI ($F = 6.51$, $p < 0.002$, $\eta^2_p = 0.036$), but not with DSI-Cognitive or DSI-Total. Number of concussions was associated with DSI-Somatic ($F = 3.01$, $p < 0.027$, $\eta^2_p = 0.022$), DSI-Vestibular ($F = 2.67$, $p < 0.047$; $\eta^2_p = 0.019$), and sleep disturbance (PSQI, $F = 5.42$, $p < 0.001$, $\eta^2_p = 0.044$), but not with DSI-Cognitive, DSI-Sensory, or DSI-Total. Three or more concussions compared with none or one previous concussion was associated with DSI-Sensory ($F = 8.56$, $p < 0.004$, $\eta^2_p = 0.022$), DSI-Somatic ($F = 8.75$, $p < 0.023$, $\eta^2_p = .023$), and DSI-Vestibular ($F = 8.65$, $p < 0.003$, $\eta^2_p = 0.022$), but not for DSI-Cognitive, DSI-Total or insomnia. Two previous concussions were not significantly different from zero or one concussion in any post-concussive symptom outcome, except for insomnia ($p < 0.004$) (Table 2).

A two-way ANCOVA with independent variables Recency of Concussion and Number of Concussions, including Previous Deployment, CES, PCL-M, and PHQ-8 as covariates, found significant or marginally significant interactions for DSI-Cognitive ($F = 4.25$, df = 2,406, $p < 0.021$, $\eta^2_p = 0.021$), DSI-Sensory ($F = 2.64$, df = 2,406, $p < 0.072$, $\eta^2_p = 0.013$), DSI-Somatic ($F = 2.95$, df = 2,406, $p = 0.054$,

Table 1. Influence of Concussion History on Emotional Tests

		Emotional tests (with all covariates included)					
		PCL-M		*PHQ-8*		*DSI-Anger*	
	N	*Mean (SD)*	p *value (ES)*	*Mean (SD)*	p *value (ES)*	*Mean (SD)*	p *value (ES)*
Any past concussion:							
No	300	27.7 (11.8)		4.8 (4.9)		1.6 (2.2)	
Yes	116	34.2 (15.4)	0.000(m)	6.3 (5.3)	0.021(s)*	2.6 (2.2)	0.002(s)*
Never	305	27.5 (11.7)		4.7 (4.9)		1.46 (2.1)	
>6 mos. ago	98	33.6 (14.8)		6.0 (5.1)		2.27 (2.4)	
<6 mos. ago	15	42.1 (17.6)	0.000(m)	9.9 (5.5)	0.001(s)*	4.31 (3.3)	0.000 (m)*
0	305	27.5 (11.7)		4.7 (4.9)		1.6 (2.2)	
1	36	32.2 (13.4)		5.7 (4.0)		2.0 (2.5)	
2	33	31.2 (14.6)		5.3 (5.1)		2.4 (2.9)	
3+	43	39.4 (16.9)	0.000 (m)	8.3 (5.4)	0.004(s)*	3.5 (2.7)	0.001(m)
0–1 vs. 3+ > [criteria]	387		0.000 OR = 2.48 [PCL-M >50]		0.027 OR = 2.19 [PHQ-8 >10]		0.001 OR = 4.36 [DSI-Anger >1SD]

PCL-M, Post-traumatic Symptom Disorder Check List, military version; PHQ-8 Primary Care Health Questionnaire; DSI-Anger, Deployment Stress Inventory; SD, standard deviation; ES , effect size; OR, odds ratio.

*Significant ($p < 0.001$) with a moderate to large effect size before including covariates of previous deployment, CES, PCL-M, and PHQ-8.

The influence of any previous concussion, recency of most recent concussion (less than or greater than 6 months since the most recent concussion), number of Lifetime Concussions (0, 1, 2, 3, or more) and three or more versus zero or one concussions on emotional and post-concussive symptom reporting, showing mean and standard deviation (SD). General Linear Model (ANCOVA) results for significance level (p value) and effect size (ES–small [s], medium [m], or large [l]) using partial eta-squared effect size (η^2_p) are based on the throughput, with Combat Exposure Survey, Deployment, PCL-M, and PHQ-8 serving as covariates (except when the covariate is itself the dependent variable). Bivariate Logistic Regression reports Wald for unique contributions and odds ratio for three or more versus zero or one lifetime concussions.

$\eta^2_p = 0.014$), DSI-Total ($F = 3.02$, df = 2,406; $p < 0.05$, $\eta^2_p = 0.015$), but not DSI-Vestibular or PSQI, with those who had three or more concussions with the most recent concussion within 6 months reporting more distress than those who had none or one concussion in the more distant past. ES were small for all analyses, likely because of insufficient power.

Binary Logistic Forward Stepwise Wald Regression was used to determine the influence of three or more concussions compared with zero or one concussion on DSI scales being one SD above the mean. Results showed three or more concussions predicting DSI-Sensory (Wald = 7.42, $p = 0.006$, OR = 1.81, CI: 1.15–2.76) and DSI-Vestibular (Wald = 4.24, $p = 0.04$, OR = 2.57, CI: 1.05–6:74), but not DSI-Cognitive, DSI-Somatic, DSI-Total, or PSQI when all covariates were included. Without covariates, all DSI subscales were significant with at least moderate ES.

In general, independent of deployment, CES, PCL-M, and PHQ-8 scores, the presence of a previous concussion was not related to post-concussive reporting, with the exception of more insomnia.

Table 2. Influence of Concussion History on Post-Concussive Tests

		Post-concussive tests (with all covariates included)												
		DSI-Cognitive		*DSI-Sensory*		*DSI-Somatic*		*DSI-Vestibular*		*DSI-Total*		*PSQ-I*		
	N	*M(SD)*	p*(ES)*	*M(SD)*	p*(ES)*	*M(SD)*	p*(ES)*	*M(SD)*	p*(ES)*	*M(SD)*	p*(ES)*	*N*	*M(SD)*	p*(ES)*
Any past concussion:														
No	300	.38(.47)		.13(.25)		.36(.33)		.15(.31)		.37(.36)		256	5.3(3.2)	
Yes	116	.57(.55)	n.s.*	.25(.40)	n.s.*	.55(.44)	.018(s)*	.30(.47)	n.s.*	.56(.46)	n.s.*	99	7.8(4.1)	.000(m)
Never	305	.38(.46)		.12(.25)		.36(33)		.15(.30)		.34(.35)		257	5.3(3.2)	
>6 mos. ago	137	.56(.52)		.21(.35)		.52(.41)		.25(.43)		.51(.42)		84	7.6(4.1)	
<6 mos. ago	16	.76(.70)	n.s.*	.53(.57)	.004(s)*	.86(.37)	.007(s)*	.59(.36)	.002(s)*	.82(.53)	n.s.*	15	8.7(3.9)	.002(m)
0	305	.38(.46)		.12(.25)		.36(.33)		.15(.30)		.37(.37)		257	5.3(3.2)	
1	36	.48(.47)		.19(.30)		.46(.39)		.21(.38)		.47(.40)		28	7.4(.4.0)	
2	33	.57(.55)		.18(.35)		.50(.44)		.21(.37)		.53(.46)		29	7.8(4.0)	
3+	43	.69(.58)	n.s.*	.37(.47)	n.s.*	.71(.43)	.027(s)*	.45(.57)	.047(s)*	.70(.48)	n.s.*	43	8.0(.4.2)	.001(m)
0–1	341	.38(.46)		.13(.25)		.37(.33)		.15(.31)		.38(.37)		285	5.5(3.3)	
Vs.3+	43	.71(.49)	n.s.*	.38(.47)	.004(s)*	.71(.43)	.003(s)*	.46(.57)	.003(s)*	.71(.40)	n.s.*	43	8.0(4.3)	n.s.*

DSI, Deployment Stress Inventory ; PSQI, Pittsburg Sleep Quality Inventory ; SD, standard deviation; ES, effect size.

*Significant ($p < 0.001$) with a moderate to large effect size before including covariates of previous deployment, Combat Exposure Survey, Post-Traumatic Symptom Disorder Check List, military, and Primary Care Health Questionnaire-8.

The influence of any previous concussion, recency of most recent concussion (less than or greater than 6 months since the most recent concussion), number of Lifetime Concussions (0, 1, 2, 3, or more), and three or more versus zero or one concussions on emotional and post-concussive symptom reporting, showing mean (M), standard deviation (SD), p value (p), and effect size (ES- small [s], medium [m], or large [l]).

Recency of concussion, number of concussions (especially having had three or more lifetime concussions), as well as the interaction between number and recency of concussions, however, was associated with worse post-concussive symptoms reporting. ES were large when covariates were not included, suggesting the synergistic effects of these covariates with concussion on post-concussive symptom reporting.

Effects of concussion on neurocognitive functioning

The effects of concussion on neurocognitive functioning were analyzed with the inclusion of covariates including previous deployment, CES, PCL-M, and PHQ-8. If significance was marginal, analysis was conducted for PCL-M and PHQ-8 covariates only or with no covariates and reported accordingly to determine the relative factors influencing neurocognitive functioning. Therefore, reported significance includes all covariates, unless otherwise indicated. Summary of findings, including Means, SD, %Correct, and TP along with significance for the relevant covariates are reported in Table 3. The most relevant metric for analysis, TP for SRT, PRT, SPD, CDS, and STN, and %Correct for GNG and CDD are used for analysis, below.

Single concussion. Having ever experienced a previous concussion (Y/N) was associated with SRT-TP ($F = 7.11$, $p = 0.008$, $\eta^2_p = 0.011$) and PRT-TP ($F = 5.82$, $p = 0.016$, $\eta^2_p = 0.009$) but only without covariates included). GNG-%, CDS-TP, SPD-TP, STN-TP, and CDD-TP were not significant, even without inclusion of any covariates. In summary, having a previous concussion (Y/N) was not associated with neurocognitive outcomes when covariates for PTSD, PHQ, and deployment experience were taken into account.

Recency of concussion. The effects of a concussion within 6 months compared with previously or never concussed was significant for SRT-TP ($F = 4.48$, $p = 0.012$, $\eta^2_p = 0.014$) and PRT-TP ($F = 4.81$, $p = 0.008$, $\eta^2_p = 0.015$), but only when no covariates were included. CDS-TP, GNG-%, SPD-TP, STN-TP, and CDD-% were not significant, even without including covariates. In summary, the effects of recency of concussion were detected by SRT and PRT only when no covariates were included, and not at all by other neurocognitive measures, possibly because of the low numbers of service members who reported a concussion within the previous 6 months. Indeed, cell sizes ranging between 11 and 16 produced power below 0.30 for these analyses.

Multiple lifetime concussions. Multiple concussions (0, 1, 2, 3, or more) were associated with SRT-TP ($F = 2.94$, $p = 0.03$, $\eta^2_p = 0.021$, with only PCL-M and PHQ-8 as covariates), marginally for PRT-TP ($F = 2.57$, $p = 0.053$, $\eta^2_p = 0.012$, without covariates), GNG-% ($F = 3.15$, $p = 0.025$, $\eta^2_p = 0.015$, without covariates), and CDS-TP ($F = 2.68$, $p = 0.046$, $\eta^2_p = 0.019$, without covariates). CDS-% SPD-TP, SPD-TP, and CDD-% were not significant, even without covariates. Because of concerns that those receiving only Rapid or Brief batteries may not have been equivalent to those receiving Standard, similar analyses were conducted with Brief subjects only, using the same covariates except substituting the PCPTSD taken by Brief subjects instead of the PCL-M.

GLM ANCOVA with covariates entered together showed that results were similar for this subsample: Number of Concussions, but not Recency of Concussion, was associated with SRT-TP, PRT-TP, GNG-%, and CDS-TP without covariates. In summary, several of the neurocognitive tests requiring simpler processing responses were positive for multiple concussion without covariates included. In all cases, results were in the expected direction; however, when all covariates were included, these trends were eliminated.

3+ Lifetime concussions. Because there was no significant difference between none and one concussions, and most often not even with two concussions, and the largest difference across outcomes was from having three or more lifetime concussions, additional analysis was conducted on three or more concussions (3+) compared with none or one concussion (0–1). A significant difference was detected, incorporating all covariates, for SRT-TP ($F = 6.57$, $p = 0.011$, $\eta^2_p = 0.017$) and GNG-% ($F = 4.43$, $p = 0.036$, $\eta^2_p = 0.012$) incorporating all covariates, PRT-TP ($F = 3.76$, $p = 0.05$, $\eta^2_p = 0.010$, with PCL and PHQ8 covariates), and CDS-TP ($F = 6.16$, $p = 0.013$, $\eta^2_p = 0.016$) with the inclusion of all covariates. SPD-TP, STN-TP and CDD-% were not significant, even without the inclusion of covariates. No interaction of recency of concussion by 3+ concussions was found. In summary, those who reported three or more lifetime concussions were worse on neurocognitive tasks requiring simple attention and simple discrimination skills, including SRT-TP, GNG-%, and CDS-TP. The effects of three or more concussions were not detected by SPD-TP or the memory tests CDD-% and STN-%.

Finally, a Binary Logistic Wald Forward Stepwise Regression with all four covariates was conducted to examine the effect of three or more compared with none or one lifetime concussions on neurocognitive functioning further than one SD from the mean. A z-score of < 1 SD was used because Receiver Operating Characteristic Curve Analysis revealed that three or more previous concussions predicted SRT-TP < 1 SD below the mean with a sensitivity of 0.91 and specificity of 0.96, and an overall accuracy of 82% ($p < 0.03$). Analysis was limited to those tests shown above to be sensitive to impairment: SRT-TP, PRT-TP, and %GNG using a cutoff of less than one SD from the mean, and including covariates scores on PCL-M, PHQ-8, CES, and Previous Deployment status.

As presented in Table 4, three or more lifetime concussions predicted neurocognitive decrement in SRT-TP (Wald = 5.47, $p = 0.019$, OR = 2.17, CI: 1.16–5.24), PRT-TP (Wald = 4.11, $p < 0.043$, OR = 1.96, CI: 1.02–3.77), and GNG-%Correct (Wald = 4.90, $p < 0.027$, OR = 2.82: CI: 1.13–7.06). From these results, it appears that simple measures of neurocognitive functioning are sensitive to the effects of three or more concussions, independent of emotional and deployment covariates.

Discussion

Given the spike in patients presenting with concussions to emergency departments over the past 5 years, thought to be because of increased public awareness of the problem, understanding persistent symptoms associated with concussion is of growing importance.[52] Toward that end, this study attempted to determine what factors are related to PPCS, especially disentangling deployment factors from emotional factors from concussion type. PPCS was examined in terms of emotional distress (PTSD, depression, and anger symptoms), post-concussive symptoms reporting (cognitive, sensory, somatic, vestibular, and insomnia), and neurocognitive functioning across a wide range of domains of speed and accuracy.

This research was distinct from earlier studies that recruited patients presenting to a clinic and evaluated a narrower range of

Table 3. Influence of Concussion History on Cognitive Tests

Cognitive tests (sig. with all covariates included or none as indicated)				
Tests	*N*	*Mean RT (SD) sig.*	*%Correct (SD) sig.*	*TP (SD) sig.*
SRT				
Any past concussion:				
No	476	332.1 (57.5)	.990 (.03)	193.4 (29.6)
Yes	167	350.2 (83.6)*none	.981 (.04)*none	185.7 (38.1)*none
Never	494	332.9 (59.0)	.990 (.03)	193.1 (29.9)
>6 mos. ago	136	347.7 (82.7)	.982 (.04)	186.6 (37.8)
<6 mos. ago	14	375.0 (17.5)*none	.975 (.06)*none	173.3 (42.7)*none
0	305	336.0 (60.2)	.999 (.04)	190.7 (30.6)
1	35	329.6 (60.7)	.995 (.01)	195.9 (20.3)
2	33	349.5 (83.9)	.980 (.05)	184.7 (39.0)
3+	42	377.9 (107.3)*all	.964 (.05)*all	173.3 (47.0)*PCL/PHQ
0–1	340	335.3 (60.2)	.999 (.03)	191.9 (30.5)
vs 3+	42	377.9 (107.3)***all	.964 (.06)***all	173.3 (47.0)**all
PRT				
Any past concussion:				
No	475	629.0 (101.1)	.985 (.02)	101.5 (14.3)
Yes	168	659.1 (152.6)*none	.977 (.03)*none	98.3 (16.5)*none
Never	493	643.7 (106.6)	.984 (.02)	101.5 (14.2)
>6 mos. ago	138	665.5 (156.4)	.979 (.03)	98.6 (16.0)
<6 mos. ago	15	717.5 (263.3)**none	.964 (.05)**none	91.6 (22.4)**none
0	305	643.7 (106.6)	.984 (.02)	99.8 (14.8)
1	36	645.3 (119.5)	.984 (.02)	101.1 (16.0)
2	32	651.27(93.3)	.987 (.02)	98.3 (12.7)
3+	42	709.6 (242.5)*none	.966 (.03)***all	94.1 (21.9)*none
0–1	341	643.9 (107.9)	.985 (.02)	99.9 (14.9)
vs 3+	42	709.6 (242.5)*all	.964 (.03)***all	93.8 (21.7)*PCL/PHQ
GNG				
Any past concussion:				
No	462	99.6 (14.8)	.990 (.03)	118.3 (19.1)
Yes	162	97.7 (17.7) n.s.	.985 (.032) n.s.	116.8 (20.4) n.s.
Never	479	538.8 (101.7)	.990 (.03)	118.4 (19.0)
>6 mos. ago	131	555.0 (135.4)	.986 (.03)	117.0 (20.3)
<6 mos. ago	15	568.5 (118.9) n.s.	.976 (.05) n.s.	111.3 (23.7) n.s.
0	478	538.8 (101.7)	.990 (.03)	118.4 (19.0)
1	51	556.5 (126.4)	.983 (.02)	116.6 (19.7)
2	37	552.3 (109.6)	.984 (.03)	115.9 (20.2)
3+	58	559.9 (110.1) n.s.	.979 (.04)*all	116.5 (22.1) n.s.
0–1	529	540.5 (104.4)	.989 (.03)	118.2 (19.1)
vs 3+	58	559.0 (154.0) n.s.	.975 (.05)*all	116.5 (22.1) n.s.
CDS				
Any past concussion:				
No	302	1346.4 (243.6)	.966 (.04)	46.9 (9.4)
Yes	115	1394.9 (296.8) n.s.	.955 (.05)*none	45.1 (10.5) n.s.
Never	307	1343.9 (243.3)	.966 (.04)	47.0 (9.4)
>6 mos. ago	96	1388.5 (272.3)	.958 (.04)	45.2 (9.9)
<6 mos. ago	15	1500.7 (422.4)*none	.936 (.06)*none	42.4 (9.7) n.s.
0	305	1344.0 (243.3)	.966 (.04)	47.0 (9.4)
1	36	1332.6 (288.8)	.960 (.04)	47.4 (10.3)
2	32	1435.7 (298.0)	.952 (.05)	44.1 (11.1)
3+	43	1439.3 (299.3)*none	.942 (.05) n.s.	43.2 (9.7)*none
0–1	341	1342.7 (248.0)	.966 (.04)	47.1 (9.5)
vs 3+	43	1439.4 (255.6)*none	.952 (.05) .n.s.	43.2 (9.7)*all

SRT Simple Reaction Time; RT, Reaction Time; SD, standard deviation; TP, throughput; PCL, Post-Traumatic Symptom Disorder Check List; PHQ, Primary Care Health Questionnaire; PRT, Procedural Reaction Time; GNG, Go-No-Go; CDS, Code Substitution Simultaneous.

TP is a measure of cognitive efficiency, based on both speed and accuracy. Higher values indicate better cognitive efficiency.

*$p<0.05$, **$p<0.01$, ***$p<0.005$ using Previous Deployment, Combat Exposure Survey (CES), PCL, PHQ as covariates.

Number of concussions (0, 1, 2, 3, or more) and Recency of Concussion (less than or greater than 6 months since the most recent concussion) reporting Mean Correct RT, SD, Percent Correct, TP. General Linear Model (ANCOVA), or Generalized Linear Modeling (for unequal variances) results for significance level with covariates are reported. Covariates are referred to as ALL (PCL/PHQ/CES/Deployment), PCL/PHQ (only), and none. Memory and spatial tests (Spatial Rotation Discrimination/ Sternberg Memory Test/ Code Substitution–Delayed Memory) were not significant, so are not included in the table.

Table 4. Effect of Three or More Lifetime Concussions on Neurocognitive Functioning

Variables in the equations

SRT-TP	*B*	*S.E.*	*Wald*	*df*	*Sig.*	*Exp(B)*
Step 2[b]						
Conc_Count_01_v_3plus(1)	−.902	.385	5.477	1	.019	2.174
PCL0SCORE	−.027	.010	7.053	1	.008	1.027
Constant	2.236	.414	29.136	1	.000	9.355

a. Variable(s) entered on step 1: PCL0SCORE.
b. Variable(s) entered on step 2: Conc_Count_01_v_3plus.

PRT-TP	*B*	*S.E.*	*Wald*	*df*	*Sig.*	*Exp(B)*
Step 1[a]						
Conc_Count_01_v_3plus(1)	.675	.333	4.113	1	.043	1.964
Constant	.048	.166	.084	1	.772	1.049

a. Variable(s) entered on step 1: Conc_Count_01_v_3plus.

GNG-%Correct	*B*	*S.E.*	*Wald*	*df*	*Sig.*	*Exp(B)*
Step 1[a]						
Conc_Count_01_v_3plus(1)	1.037	.468	4.901	1	.027	2.819
Constant	−2.156	.234	84.805	1	.000	.116

a. Variable(s) entered on step 1: Conc_Count_01_v_3plus.

Binary Logistic Wald Forward Stepwise Regression examining the effect of three or more lifetime concussions on neurocognitive functioning: Simple Reaction Time Throughput (SRT-TP), Procedural Reaction Time Throughput (PRT-TP), and Go-No-Go %Correct (%GNG) using a cutoff of less than one standard deviation from the mean, and including covariates scores on Post-Traumatic Symptom Disorder Check List-Military; Primary Care Health Questionnaire; Combat Exposure Survey, and Previous Deployment status. Only final model step is presented.

outcomes in that it assessed a cohort of active duty US military service members who were fit for duty and participating in daily work activities, with assessment of previous deployment, combat exposure, emotional distress, post-concussive symptoms, and neurocognitive functioning to examine persistent effects of concussion. Further, by including previous deployment, combat exposure, PTSD, and depressive symptoms as covariates to determine the unique contribution of concussion, this approach was able to explore the theory that PPCS is because of emotional issues alone.

Results showed that recent deployment, higher CES, PCL-M, and PHQ8 each had an effect on concussion number and recency, emotional distress, and post-concussive symptom reporting, as well as for Attention-Discrimination type neurocognitive tasks, but not for memory-dependent tasks. The presence of a previous concussion as well as recency of concussion had an effect on emotional distress. The presence of a previous concussion was not related to post-concussive symptom reporting, with the exception of insomnia, nor to neurocognitive functioning. Recency and number of concussions, however, were associated with post-concussive symptom reporting, and number of concussions was related to Attention-Discrimination type neurocognitive functioning.

Having had three or more lifetime concussions was associated with the worst scores for depression, PTSD, anger, post-concussive sensory, somatic, and vestibular symptoms, and was predictive of the lowest performers on simple cognitive tasks. Although subjective cognitive complaints and insomnia symptoms are associated with three or more lifetime concussions with a moderate effect size, these associations were not sustained when deployment, CES, PTSD Sx, and Depressive Sx were considered as covariates. This suggests that persons with multiple concussions may complain of cognitive and insomnia symptoms, but at least in this sample, they appear to be primarily from emotional factors.

Our findings support earlier reports that deployment was associated with worsening neurocognitive[32,40] and emotional[53] functioning. We also found support for previous research that depression and PTSD are strong predictors of post-concussive symptoms, including neuropsychological and self-reported post-concussive symptoms.[18,20] In addition, findings in this study sample for the most part supported earlier research that failed to find the presence of a previous concussion to be related to post-concussive symptom reporting or a decrease in neurocognitive efficiency, once the contributions of deployment, combat exposure, PTSD, and depressive symptoms were removed.

The presence of previous concussion, however, independent of previous deployment or combat exposure, was associated with worse levels of PTSD, depression, and insomnia, all with moderate effect sizes. Moreover, the presence of three or more lifetime concussions was associated with a decrease in cognitive efficiency and an increase in post-concussive symptoms, independent of PTSD and depressive symptoms or likely diagnosis. Specifically, recency of concussion was associated with worse emotional and post-concussive symptoms, especially for those who had three lifetime concussions.

There was insufficient power to determine if having a concussion within the previous 6 months was a further contributor to cognitive functioning, but given that the effects of multiple concussion were consistently worse for those with a recent deployment, and the interaction of recency and number of concussions in other domains, the impact of recency of concussion on post-concussive symptoms is worthy of continued examination. Indeed, a recent study of active duty soldiers showed that recent concussion, independent of injury mechanism or combat exposure, is predictive of persistent post-concussive complaints.[54]

Thus, although these findings are consistent with research that failed to find independent evidence for the presence or absence of

previous concussion, the evidence of recent and multiple concussion across a range of emotional distress, post-concussive symptom, and neurocognitive functioning is in contrast with other studies that failed to find a unique contribution for concussion across a wide range of persistent post-concussive symptoms.[18,55] Possible reasons for this may include the failure of other studies to include both objective and subjective assessments of functioning, assessment of a wide range of PPCS including neurocognitive, self-report emotional and somatic symptoms, and, most importantly, the distinction between single and multiple concussion, and its recency. Further, the assessment of deployment and combat exposure has rarely been used to tease out the specific effects of combat deployment from other factors influencing PPCS outcomes in active duty personnel. This may have implications for civilians as well in that severity of trauma exposure may need to be included in any assessment of PPCS.

Although we included previous deployment and CES as covariates, we wanted to insure that the results based on the entire sample were also seen in the recently deployed troops only (deployed within the previous 6 months). Analysis of the effects of three or more lifetime concussions in this subsample showed a similar pattern to what is reported with the entire sample on emotional and post-concussive symptoms as well as neurocognitive functioning.

Also of note, recently deployed service members in our sample had slower reaction times across several neurocognitive tests compared with never or previously deployed service members. Vasterling and coworkers,[32] however, found post-deployed service members responded faster in several neuropsychological tests than they did pre-deployment, which they attributed to a hyperaroused nervous system. Perhaps this is because of differences in testing methods; we used an NCAT capable of assessing each response for speed and accuracy, whereas Vasterling used paper and pencil measures to determine overall speed. Moreover, these authors assessed service members sooner after deployment, when their nervous systems may have been in a different state than several months later. Certainly, more longitudinal and cross-sectional research on post-deployed service members is needed to shed light on neurocognitive performance after stressful deployments.

The fact that this neurobehavioral battery was generally sensitive to factors (despite that covariates often accounted for most of the variance) shows that such neurobehavioral batteries hold promise as a useful tool for detecting alterations in cognitive functioning from a variety of reasons, whether emotional, physical, or because of fatigue. It is noteworthy that those tests relying more on attention and simple discrimination (SRT, PRT, GNG, and CDS) were more sensitive to the effects of recency and number of lifetime concussions than were SPD or the memory-dependent tests (CDD, STN). This may be because of the increased time to answer these latter tasks along with the ability to rally compensatory effort and strategies. By contrast, the simpler tasks needed to be answered in a faster period and relied on more primitive processing skills, thus not permitting for increased effort or compensatory mechanisms to be used.

Based on these results, this study shows that the tests contained within this neurobehavioral battery, especially those relying on attention and simple discrimination, may be worthwhile administering to military members to determine how they are functioning so that early detection of suspected problems can aid in getting them the care they need. Although covariate analysis was conducted to demonstrate the unique contribution of concussion, PTSD, depression, and other factors influencing PPCS, it is important to appreciate that the combination of concussive and psychological factors are frequently co-occurring, likely enhancing symptoms, and presenting unique challenges to diagnosis and treatment.

All postconcussive subjective symptoms, including insomnia, seem to be shared by multiple concussion, PTSD symptoms, depressive symptoms, and combat experience. Yet multiple concussion by itself appears to contribute less to cognitive complaints and insomnia than it does to sensory, somatic, and vestibular complaints. This is a unique finding in the literature, possibly because previous studies have inadequately controlled for covariates that influence these subjective symptoms. If this finding is replicated in other samples, then these complaints may need to be more heavily weighted to better understand the unique contribution of concussions to persistent symptom reporting.

From the perspective of treating persistent postconcussive symptoms, however, distinguishing between the independent effects of concussion from emotional factors may not always be desired. Given that concussion is associated with increased odds of PTSD (OR = 2.5), depression (OR = 2.2), and anger (OR = 2.4), independent of combat experience (Table 1), it is important to appreciate emotional factors as frequently comorbid with multiple concussion. Thus, clinicians' consideration of the effects of concussion on PPCS for determination of illness severity, and possibly even for treatment planning, need not be as analytically separated as is necessary for research.

Research to improve understanding of the unique contributions of various components of the wounds of war, as well as ways to better appreciate their interaction resulting in the gestalt experienced by the veteran, is necessary. Therefore, although it is important to determine the unique contributions of these various factors, it is also important to appreciate that separating them may lead to an underestimation of their combined effects.

Based on these results, it seems premature to recommend cessation of assessments for concussion post-deployment. Further, because there is so much comorbidity in this population, further research identifying the independent and combined causes of persistent symptoms should prove useful in both evaluating the functioning of the individual, as well as supporting the development of interventions that are tailored to the needs of those with specific symptom clusters.[56] Future research that follows a cohort prospectively to better understand the time-course and causality of symptoms associated with concussion, as well as identifying if the context of the concussion (such as combat, assault, or accident), will also be of importance in the understanding and treatment of concussion and associated symptoms.

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An Evaluation of the Consistency and Reliability of the Defense Automated Neurocognitive Assessment Tool

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Abstract

A durable, portable, and field-hardened computerized neurocognitive test (CNT) called the Defense Automated Neurobehavioral Assessment (DANA) tool was recently developed to provide a practical means to conduct neurological and psychological assessment in situ. The psychometric properties of the DANA have been previously described. This present work discusses the test–retest reliability of the DANA Rapid test battery, as administered to a homogeneous population of U.S. Air Force Academy football team players (N = 162) across the duration of the season. The intraclass correlation coefficient (ICC) metric of the DANA is compared with that from two different CNTs recently reported in Cole et al., and the implications of using the metric to interpret comparative test reliability among different CNTs are discussed.

Keywords

reliability, cognitive assessment, screening, traumatic brain injury, concussion, sports concussion, CNT

Introduction

Although the efficiency and utility of a neurocognitive assessment tool is determined by its internal consistency, and the measure of test–retest reliability is typically described as the foundation on which a test's validity is established (Cole et al., 2013), a consistent methodology for quantifying reliability is not clearly demonstrated in the current neuropsychology literature. Disconcertingly, recent works have found that the reliability coefficients of computerized neurocognitive tests (CNTs) tend to fall below the bar of ''clinical acceptability'' (Broglio, Ferrara, Macciocchi, Baumgartner, & Elliot, 2007; Cole et al., 2013; Resch et al., 2013; Segalowitz et al., 2007). Differences in the characteristics of test batteries, differences in the design of test–retest studies, and insufficiently explained and non-standardized methods of analysis have all served to confound the matter of clearly defining a quantifiable measure of reliability (Christie, Kamen, Boucher, Inglis, & Gabriel, 2010; Weir, 2005).

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The definition of the reliability coefficient is both contextual and application-specific (e.g., Baumgartner, 1969; Feldt & McKee, 1958; Streiner & Norman, 1995), and as a result, any given reliability coefficient is not a universal measure of reliability. For example, there is still a pervasive reporting of Pearson's *r* to assess reliability even though its use is actively discouraged due to the model's inherent disregard for systematic error (Baumgartner, 2000; Bedard, Martin, Krueger, & Brazil, 2000; Kroll, 1962; Ludbrook, 2002; Safrit, 1976) and is therefore an inappropriate metric for certain applications.

In neuropsychology, the intraclass correlation coefficient (ICC; as formalized by Shrout & Fleiss, 1979, and then updated by McGraw & Wong, 1996) is often reported as the stand-alone metric of test–retest reliability. By definition, the ICC calculation entails six different possible configuration parameters by which the coefficient is determined, and each model's estimate is unique. A side-by-side comparison of the methods of recent works (such as Broglio et al., 2007; Cole et al., 2013; Resch et al., 2013) reveals that the ICC approach is often not applied in a standardized way, possibly because the ICC model itself is not well-understood. Implicit disagreement between research groups pertaining to which ICC model most accurately describes the test–retest design may stem from confusion around the applicability of the ICC model as developed for inter-rater reliability rather than for test–retest reliability (Weir, 2005).

These two types of reliability describe distinctively different situations: Inter-rater reliability tests the hypothesis that a heterogeneous group of judges (the raters) similarly rate the same set of subjects (the ratees) across multiple testing sessions. Test–retest reliability tests the hypothesis that the subjects themselves (the ratees) perform the same way across the sessions and assumes the raters (the computers) are the same. As a result, the ICC was designed to be relatively insensitive to within-subject, session-to-session variability, and is thus only informative of test–retest reliability *by proxy*. Owing to this detail, other fields (e.g., exercise and sports science, sports medicine, and physical therapy) report the ICC along with a precision metric provided by the standard error of the measurement (SEM) that offers an absolute bound on the measurement of interest (Denegar & Ball, 1993; Learmonth, Dlugonski, Pilutti, Sandroff, & Motl, 2013). It is crucial to note that for the purpose of comparing the reliability of different CNTs, it is particularly important to report the reliability coefficient accompanied by a precision metric.

The SEM carries the same units as the measurement of interest (e.g., throughput or reaction time) and it is informative of within-subject reliability. It can be obtained from the reliability coefficient (this method provides the coefficient's precision), or independently of the reliability coefficient, from the square root of the mean square error. In either case, the minimum difference (MD) is directly constructed from the SEM and describes the minimum amount of change in results required to be considered a real effect and not an artifact of associated error (Weir, 2005).

This work describes consistent test and retest measurements of the Defense Automated Neurobehavioral Assessment (DANA) test as administered to a homogeneous population of U.S. Air Force Academy football team players ($N = 162$) through time points across the season. The ICC metric of the DANA is compared with that from two different CNTs recently reported in Cole et al. (2013), and the implications of using the metric to interpret comparative reliability among different CNTs are discussed.

Method

The DANA Rapid Tests and Administration

The psychometric properties of the DANA test batteries have been previously described and evaluated (Lathan, Spira, Bleiberg, Vice, & Tsao, 2013). Data for this study were collected under the U.S. Air Force Academy performance improvement protocol. The DANA Rapid test

Table 1. Summary Statistics for Each Testing Session Date (Denoted as $T_{1,2}$).

		<TP>		*SD* <TP>			*R*		
Battery	Subtest	T_1	T_2	T_1	T_2	*n*	LB	UB	MD
DANA	PRT	102.9	106.8	13.02	12.57	89	0.75		18.04
							0.60	0.84	
	RT	192.4	198.3	26.77	23.54	87	0.81		32.34
							0.69	0.87	
ANAM4	PRT	97.62	103.56	13.10	10.31	50	0.51		25.42
							0.28	0.69	
	RT	86.88	91.38	11.46	12.76	50	0.60		22.37
							0.39	0.75	
ImPACT	RT	0.60	0.61	0.08	0.09	44	0.53		0.17
							0.28	0.71	

Note. Reported mean throughput (<TP>) is the mean throughput of *n* total subjects (matched for test and retest), and *SD* <TP> is the associated standard deviation of the mean throughput of *n* total subjects. For the DANA data, *R* was calculated by the way of Equation 2, presented with LB and UB (constructed in the 95% confidence interval). With respect to the ANAM4 and ImPACT data listed here from Cole et al. (2013), the ICC model used to calculate *R* which was not reported in that work. Note that the reported metric for ImPACT is not <TP>, but rather ImPACT's composite score. The MD is calculated from Equations 3 and 4, using the greater standard deviation between the two time points per subtest, per test battery. TP = throughput; LB = lower bound; UB = upper bound; MD = minimum difference; DANA = Defense Automated Neurobehavioral Assessment; ANAM = Automated Neurobehavioral Assessment; ImPACT = Immediate Post-Concussion Assessment and Cognitive Testing; RT = Reaction Time; PRT = Procedural Reaction Time.

battery consists of three cognitive tests given in succession, each of which measures reaction time (see Table I in Lathan et al., 2013). On a given testing date, U.S. Air Force cadets participating on the Air Force Academy football team were administered the DANA Rapid along with a demographic survey that were both loaded onto a collection of identical mobile devices (Trimble Nomads, model 900S). The test administration time totaled about 5 min.

Data were collected at the beginning of the season on August 22 to 24, 2012, in the middle of the season on November 6 to 7, 2012, and at the end of the season on April 30 to May 1, 2013. If a subject took more than one administration of a test in any given testing session, then only the first administration was included in the following analysis. In addition, a subject must have correctly responded to more than 66% of the test stimuli. Test–retest reliability was calculated from the scores of the first test (or only test) administered per testing date, tabulated for the same subjects across the season. The test–retest reliability (reported ICC) of the DANA is compared with that from two of the CNTs reported in Cole et al. (2013), for comparable neurocognitive subtests. The retest duration specified in Cole et al. was 21 to 42 days post-baseline, and thus for better comparison, the shortest period retest of the DANA that was administered is reported, approximately 77 days post-baseline (August-November administrations).

For each of *n* subjects, a subject's mean throughput (<TP>, with units of min^{-1}) was calculated from correctly answered mean response time data (<$\text{RT}_{\text{correct}}$>, with units of milliseconds),

$$<\text{TP}> = \frac{\frac{\text{total}_{\text{correct}}}{\#\text{trials}}}{<\text{RT}_{\text{correct}}>} \times 60,000. \quad (1)$$

The factor of 60,000 converts milliseconds to minutes. To assess consistency in <TP> in the DANA data across time points, a multi-way repeated-measures ANOVA was performed for all of the subjects across testing sessions, per subtest.

The ICC

In essence, the ICC is a relative (unitless) measure of test error with regard to between-subject variability. The interpretation of the ICC is that it represents the score variance that is attributable to the variability between subjects and the remainder of the variance is attributable to error. Because systematic differences can explain variability in the data, the choice of ICC model parameters is dependent on the study design and the characteristics of the test subjects. Test–retest designs lend themselves to two-way model analyses, and for situations in which the testing devices are not themselves variable (identical and electronically stable), use of the average measures parameter is appropriate as it will not over-compensate for error and thus artificially deflate the resulting coefficient (Christie et al., 2010; Weir, 2005). The two-way, average measures model is given as,

$$\mathrm{ICC}\{2,k\} = \frac{\mathrm{MS}_S - \mathrm{MS}_E}{\mathrm{MS}_S + \frac{k(\mathrm{MS}_T - \mathrm{MS}_E)}{n}}, \tag{2}$$

where $\mathrm{MS}_{S,E,T}$ denote the mean squares (derived from the sum of squares resulting from a repeated-measures ANOVA calculation) of subjects (S), systematic error (E), and trials (T); k is the number of test administrations and n is the number of subjects. On the DANA data presented in this work, the ICC was tabulated using a *MATLAB* script (Salarian, 2008) that follows the formalism in McGraw and Wong (1996).

SEM and MD

The SEM is an absolute index of reliability and provides insight into the session-to-session noise in a given set of data. It carries the same units as the measurement of interest and can be interpreted as the reliability within individual subjects (Shrout, 1998; Weir, 2005). The SEM can be found both from the ICC, or estimated independently from the ICC as the square root of the mean square error (MS_E; Eliasziw, Young, Woodbury, & Fryday-Field, 1994; Hopkins, 2000; Stratford & Goldsmith, 1997; Weir, 2005). Following the formalism in Weir (2005), from the ICC, the SEM is written as,

$$\mathrm{SEM}_{\mathrm{ICC}} = SD\sqrt{1 - \mathrm{ICC}}, \tag{3}$$

where SD is the standard deviation of subjects' scores.

Alternatively, the ICC-independent form of the SEM is calculated using the MS_E, related to the sum of squares error, SS_E, found from the ANOVA calculation, $\mathrm{MS}_E = \mathrm{SS}_E/((n-1)(k-1))$, where n is the number of subjects and k is the number of test administrations. The ICC-independent form of the SEM is the square root of the MS_E ($\mathrm{SEM} = \sqrt{\mathrm{MS}_E}$).

In either case, the SEM is the basis of the MD index or the minimum increment of observable change that warrants consideration as a real change in score and likely not attributable to error:

$$\mathrm{MD} = \mathrm{SEM} \times z \times \sqrt{2}, \tag{4}$$

where the $\sqrt{2}$ is an artifact of the standard error of the difference of two score results from test and retest administrations. In Equation 4, z is the distribution score used to construct the confidence interval. In this work, the MD is reported as an absolute index for reliability, constructed in the 95% confidence interval for which $z = 1.96$.

Results and Discussion

The results from all tested batteries are captured in Table 1. The reliability coefficient measured for DANA, for matching subjects across test and retest sessions, is found to be higher than those from both the Automated Neurobehavioral Assessment Metric (ANAM), and the Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) tools, and comparatively, the DANA exhibits a reliability coefficient within tighter upper and lower bounds than both ANAM and ImPACT. A multi-way repeated-measures ANOVA was performed for all of the subjects per DANA subtest, grouped by testing session, and the results (not reported, for brevity) showed that the marginal means of <TP> in the retest sessions are not significantly different from those in the first test sessions ($p > .05$). For a homogeneous, non-clinical population, the average throughput per subtest is not expected to change across testing sessions; in other words, the expectation for test reliability as performed on healthy and unvaried subjects is that the results of the retest administration should show no statistically significant change from the results of the first test administration. The result of the ANOVA is interpreted as a demonstration of consistency across test and retest sessions.

The tabulated MD for each subtest is based on the reported ICC coefficient for each test and battery, and the greater reported standard deviation between the two time points. In this context, the MD can be interpreted as the minimum amount of change in the population's score necessary to alert a statistically significant decrease or increase in test performance. The MD for DANA per subtest is approximately 17% of the <TP>, whereas the MD of both ANAM and ImPACT are approximately 24% and 27% of the <TP>, suggesting that, for the timescale reported here, DANA is a more sensitive measure to changes in test performance. In other words, a smaller proportional MD suggests that the measurement it describes is more sensitive to change and less confounded by error than a measurement with a proportionally larger MD.

The reliable change index (RCI) has been suggested as an alternative method to test–retest reliability, and several methods for determining the RCI have been published previously (e.g., Bruggemans, de Vijver, & Huysmans, 1997; Chelune, Naugle, Luders, Sedlack, & Awad, 1993; Jacobson & Truax, 1991; Moritz, Iverson, & Woodward, 2003; Temkin, Heaton, Grant, & Dikmen, 1999). Each of these methods distinctly relies upon the calculation of a reliability coefficient, arrived at by way of the ICC or by Pearson's r, or both. The aforementioned issues that arise from a non-standardized approach to arriving at the reliability coefficient serve to confound the interpretation of a RCI, specifically if more than one measure of reliability is calculated for any given test. For example, two measures of reliability are presented in Cole et al. (2013) and the standard error of the difference (S_{diff}, a precursor to the RCI) is tabulated using whichever measure is greater. When distinct disagreement exists between each measure within a given test, and/or when comparing tests that were measured using different reliability models, this approach is misleading. Under such circumstances and if the ICC is the calculated reliability measure, the ICC-dependent form of the SEM can provide an absolute bound on the reliability coefficient, or alternatively, the ICC-independent form of the SEM provides a bound on the measurement error. In either case, the resulting MD is found to be a consistent index for reliable change.

Conclusion

The DANA Rapid test battery was administered to cadets of the U.S. Air Force Academy football team before the commencement of the season and again during the season. The test–retest reliability of the DANA tool was evaluated and it was found that the test is consistent between test and retest sessions administered within approximately 77 days. Owing to the non-standardized practices of measuring test–retest reliability, both reporting the ICC along with a

precision metric and utilizing alternative methods to arrive at a RCI are suggested, such as with the MD approach, which is described in the ''SEM and MD'' section.

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Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: AnthroTronix Inc. is the developer of the Defense Automated Neurobehavioral Assessment (DANA) tool.

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Impact of Caffeine on Neurocognitive Performance During Sleep Deprivations Using the Defense Automated Neurobehavioral Assessment (DANA)

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Introduction

Caffeine is commonly used to alleviate the effects of sleep deprivation. A specific population that must perform while sleep deprived is the military. Many military operations require convoys to travel across flat desert terrain in order to accomplish various tasks. There are specific regulations as to the distance between vehicles that must be maintained, and speed at which vehicles can be driven within these convoys. Driving with a specific distance between, a slower speed and in an unaesthetic, repetitive landscape can become boring and monotonous. If a fatigued military truck driver is unable to stay alert on-duty the safety of the driver, the passengers and the rest of the convoy is at risk. This study serves to characterize the effects of sleep deprivation with dull tasks and examine the ability of caffeine to mitigate these effects. The Defense Automated Neurobehavioral Assessment (DANA) Rapid battery and a driver simulator were employed to measure the effectiveness of a multiple-dose caffeine administration paradigm to maintain vigilance during 2 nights of sleep deprivation. This poster focuses primarily on performance of the DANA tasks.

Methods

Participants and Design

Participation in this study was voluntary and informed consent was received from each subject. The study was proctored as a double-blind group design, in which 24 participants were randomly assigned into 6 groups of 4. There were two possible conditions to which the groups could be assigned: placebo or caffeine. Each group was randomly assigned to receive a caffeine or placebo administration.

Study subjects spent a total of 4 days and 3 nights in the sleep laboratory. Subjects were given a baseline sleep saturation from 10pm to 8am, which was followed by 49 hours of sleep deprivation/wakefulness. Caffeine was administered in 2-hour intervals—specifically at 0100, 0300, 0500, and 0700—on both nights of sleep deprivation. Performance results from the caffeine group were compared to results from the placebo group.

The primary task subjects participated in was a 40-minute driving simulator (SIM) designed to mimic the Australian outback. The simulator has seats mounted on motion actuators. This specific environment was chosen because the terrain is flat, repetitive and barren. The monotony in this simulation allows a more accurate examination of caffeine's ability to diminish the effects of sleep deprivation when performing a boring task.

After completing the driving simulation, each group performed a 5-minute PVT followed by the DANA Rapid. The DANA Rapid included a battery of three neurocognitive assessments to note: Simple Reaction Time (SRT), Procedural Reaction Time (PRT), and Go/No Go (GNG). There were a total of 18 administrations per subject and the last administration from Day 1 was used as the baseline. Placebo and caffeine groups were evaluated for statistical significance in reaction time needed to make correct responses and the number of response lapses for each test. A lapse for the SRT was >900ms; for PRT >2000ms and for GNG >1500ms. For the SIM task the number of crashes during each session was used as the primary variable for this presentation.

Measures

Defense Automated Neurobehavioral Assessment – Rapid (DANA) –Subjects completed the Rapid battery which consists of assessments of Simple Reaction Time (SRT), Procedural Reaction Time (PRT), and a Go-No-Go (GNG) task.

Driving simulator – Subjects completed a 40 minute driving simulation that was designed to reflect the environment in which on-duty military personnel are tasked to drive in. The simulator was a full motion platform with audio ques.

Figure E
An example of a soldier completing the DANA Rapid Battery

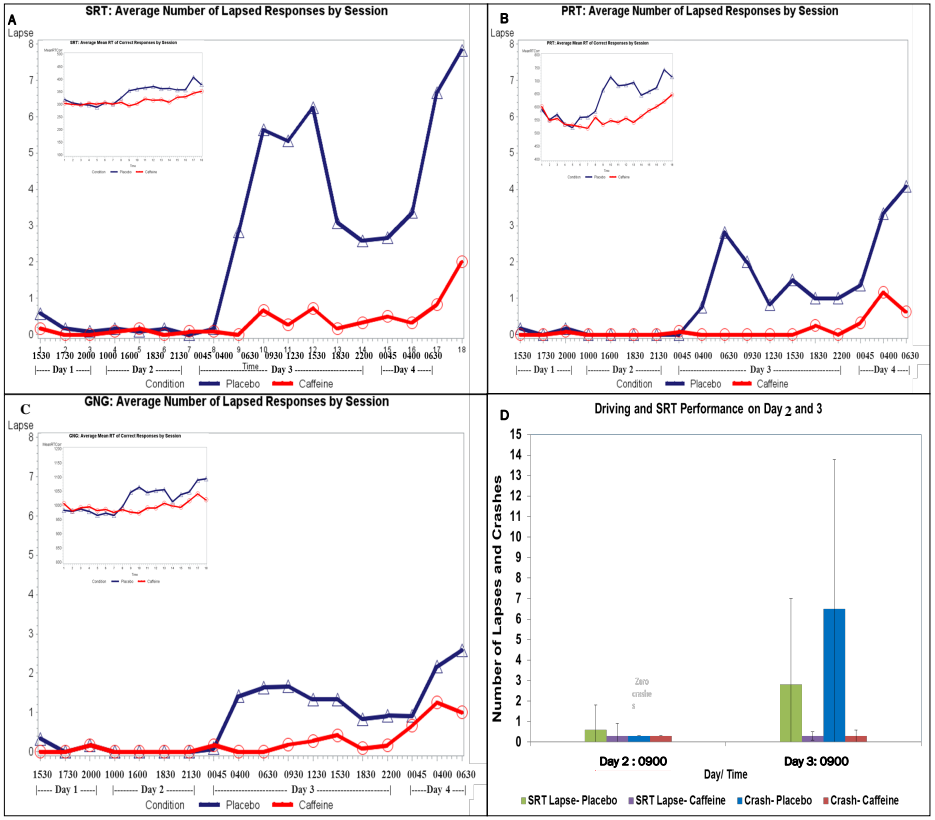

Figure A-D (to be read left to right)

A) SRT among caffeine and placebo group are comparable until subjects are sleep deprived. The placebo condition jumps from 0 lapses in the 8th DANA administration to nearly 6 lapses in the 9th. The caffeine condition holds constant between the 8th and 9th administrations. From the 8th test administration through the 18th both conditions increase their number of lapses but the placebo group has more lapses than the caffeine at every administration.

B) PRT is the same between placebo and caffeine conditions for the first two days. The placebo condition has 0 lapses at the 8th administration and 3 lapses by the 10th. The caffeine condition holds 0 lapses until the 14th administration where <1 lapse occurs. At every administration point during sleep deprivation the placebo group has more lapses than the caffeine group.

C) GNG experienced the least obvious differences between conditions. While there is still an increase in lapses seen within the placebo condition compared to the caffeine condition, the differences are smaller. Between administrations 8 and 14 there is the greatest difference between conditions with placebo having 2 lapses in GNG at administration 10 and caffeine having 0 lapses at the same gathering point. At administration 16 placebo and caffeine groups are most similar during the sleep deprivation period, seeing 1 lapse each.

D) Figure D takes measurements from two points-in-time to see if the number of SRT lapses gathered from the DANA Rapid correspond to the number of crashes seen in the driving simulation. At baseline, both conditions are performing with <1 lapse or crash. At day 3 the placebo condition has 3 lapses in SRT performance and 7 crashes in the driving simulation, while the caffeine condition still holds <1 lapse and crash. The placebo condition had a 6-fold increase in their number of lapses in SRT performance and a 7-fold increase in their number of crashes on day 3, as compared to baseline.

Lapses for the SRT are responses >900ms; for PRT >2000ms and for GNG >1500ms.

*SRT, PRT and GNG defined under measures

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Results

Repeated measures ANOVA (analysis of variance) were used in order to determine a difference in performance. Difference in performance was measured by evaluating mean reaction time of correct responses (DANA) and number of crashes between the placebo and caffeine groups (SIM). Additionally, logistic regressions were used on lapsed responses in order to determine the odds ratio when given placebo compared to caffeine.

For the DANA subtests, the repeated measure ANOVA identified a statistically significant difference in mean reaction time between placebo and caffeine groups. For both SRT and PRT, subjects in the caffeine condition performed faster by 28 ms (p=0.0433)and 68 ms (p=0.0216), respectively (See Figs A & B). While the number of lapsed responses was higher in the placebo group for the GNG, this was not significant (Fig C).

The logistic regression analysis showed significant results for all three subtests. Subjects were 4 times more likely to have a lapsed response for SRT, 5 times more likely for PRT, and 3 times more likely for GNG. Towards the end of the second night many of the subjects needed to be woken up to take the DANA.

Currently, only data from sessions 1 and 9 were available for analysis from the driving simulation. For the driving simulation, the repeated measures ANOVA resulted in a statistically significant difference in the number of crashes between placebo and caffeine groups (p=0.0154). As illustrated in Fig D the placebo group committed 3 more crashes (mean) as compared to the caffeine group. The logistic regression analysis was also significant with placebo subjects 23 times more likely to have crashed as compared to the caffeine group.

Summary/Discussion

Figures A-C compare placebo and caffeine groups by their respective number of lapsed responses. Groups were analyzed by lapses rather than speed because lapses are an accepted indicator of when a task cannot be performed correctly. Speed analysis focuses on the amount of time it takes to make the correct response, but does not evaluate incorrect responses, which leaves a considerable amount of data unrepresented. There is a speed-accuracy tradeoff in human behavior where people will reduce speed in order to increase their accuracy. An analysis using lapses account for this adjustment, while a speed analysis does not.

Even though the effects of SRT and GNG are statistically significant, they may not be operationally significant since the subjects' performance declined by less than 50ms in the post treatment measures. However, this may be due to the use of only the correct responses for this measure. It is also possible that this small difference is due to the nature of going from a monotonous driving task to a different task that required an outside stimulus (i.e. being handed a device) which has an awakening quality to it. This non-significance could also be due to small sample size.

An increased number of lapses signals decreased attention during a task. There was a 6 fold increase in the number of lapses between days 1 and 3 in SRT performance for the placebo condition. If 3 lapses were seen during the SRT task (which runs for 2minutes) on day three, we could expect to see 60 lapses during the 40 minute driving simulation. The data gathered from sessions 1 and 9 suggests an increase in SRT performance lapses could indicate an increase in poor driving performance due to sleep deprivation. On day 3 the placebo condition saw a 7-fold increase in the number of crashes during the driving simulation, as compared to their baseline performance on day 1. While lapses in the DANA do not indicate crashes, they do indicate decreased performance. If data from subsequent sessions supports what we report here then performance on the DANA may be useful as an indicator of driving performance while sleep deprived.

It is important to note that some of the placebo subjects were experiencing micro sleep and required awakening at the end of the SIM task in order to complete the PVT and DANA. This arousal could have altered the number of lapses that would have otherwise been seen and may have had an impact on DANA performance. Also, there is a certain degree of intrapersonal variation within test subjects. Some subjects may have been more or less caffeine sensitive than others as well as their individual sensitivity to sleep deprivation. These differences may account for how the variation in performance observed here.

In conclusion, even after two nights of sleep deprivation, caffeine maintained performance on the DANA tasks and simulator driving performance as compared to placebo.

Longitudinal evaluation using the recently developed Defense Automated Neurobehavioral Assessment (DANA) tool of the cognitive impact of Electroconvulsive Therapy (ECT) in the treatment of Major Depressive Disorder

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The Defense Automated NeuroBehavioral Assessment (DANA) is a clinical assessment tool that an AnthroTronix-led team developed for the Department of Defense

Introduction

Major Depressive Disorder (MDD) in active military personnel and veterans has been a major source of morbidity and mortality. MDD is often associated with cognitive impairment[1]. Little is understood about the cognitive effects of electroconvulsive therapy (ECT) during the treatment course among patients with MDD. Our study represents a novel, automated assessment of the effect on cognitive functioning of patients receiving ECT treatment for MDD.

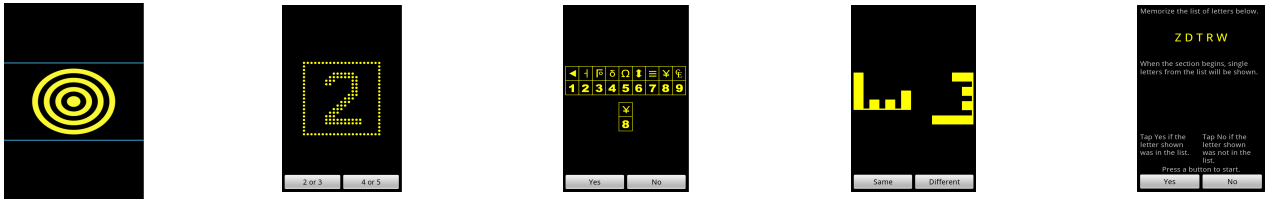
Objectives

The objectives of this study were to measure cognitive changes in MDD patients during their course of ECT treatment. We correlated cognitive measures obtained by administering DANA with results of Mini Mental Status Examinations (MMSE).

Materials and Methods

- The neurocognitive and psychological assessment battery was conducted on a 32GB Samsung Galaxy v8.9 electronic tablet with Defense Automated Neurobehavioral Assessment (DANA) software. DANA is a new neurocognitive assessment tool that includes a library of standardized cognitive and psychological assessments[2,3].
- The tablet is easy to use, portable, reliable, and provides objective, immediate, and quantitative data. All tests included in the DANA assessment meet the requirements of the American Psychological Association's standard for tests and measurements and all tests are in the public domain.
- Components of the DANA cognitive assessment battery used for the study were administered in the following order: simple reaction time 1 (SRT1), procedural reaction time (PRT), code substitution learning simultaneous (CDS), spatial discrimination, Sternberg memory search (STN), and simple reaction time 2 (SRT2) (Figure 1). Data were obtained from cognitive assessments administered twice per week and Mini-Mental Status Exam (MMSE) assessments administered 2-3 times per week (Table 2).
- **Inclusion Criteria:** Patients with major depression undergoing ECT for major depression on the psychiatry unit at the Johns Hopkins Hospital were included in the current study. Patients were either male or female, ages 18 and above.
- **Exclusion Criteria:** Demented patients incapable of completing DANA cognitive assessments were be excluded from the study, as were patients with active comorbid substance abuse disorders.
- This study was approved by the Johns Hopkins IRB and The US Army Medical Research and Materiel Command (USAMRMC), Office of Research Protections (ORP), Human Research Protection Office (HRPO) approved the subject protocol on 4 November 2013.

Figure 1: Screen shots for DANA cognitive assessments



Simple Reaction Time (SRT)
- The subject taps on the location of the yellow symbol as quickly as possible each time it appears.
- Assesses pure reaction time.

Procedural Reaction Time
- The screen displays one of four numbers of 3 seconds.
- Subject presses on a left button ("2" or "3") or right button ("3" or "4") depending on the number presented.
- Choice RT measure of accuracy, RT, & impulsivity which targets simple executive functioning with easy decision-making capabilities

Code Substitution Learning
- Subjects refer to a code set of 9 symbol-digit pairs that are shown across the upper portion of the screen.
- A sequence of single symbol-digit pairs is shown below the key, and the subject indicates whether or not the single pair matches the code by pressing Yes or N.
- Assesses visual scanning and attention, learning, and immediate recall.

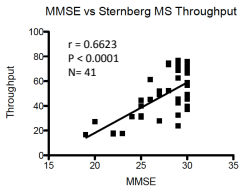
Spatial Discrimination (SPD)
- Pairs of four-bar histograms are displayed on the screen simultaneously, and the subject is requested to determine whether they are identical.
- One histogram is always rotated either ±90 degrees with respect to the other histogram.
- Assesses visuospatial analytic ability.

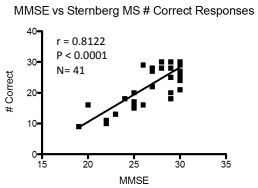
Sternberg Memory (STN)
- The subject memorizes a set of five letters, after which letters appear on the screen one at a time, and the subject determines if the letter on the screen is a member of the memory set.
- Assesses working memory.

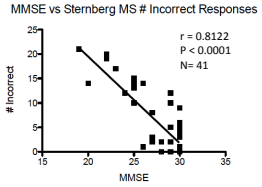
Results

Table 1: Characteristics of study sample (n = 6)

Parameter	% or Mean
Female (%)	67
Age (years old)	43.2
White (%)	100







	PROCESSING SPEED SENSITIVE				
Reaction Time 1	RT1 Mean RT Correct Responses	RT1 Median RT Correct Response	RT1 Mean RT	RT1 Median RT	RT1 Throughput
	-0.7197	-0.7432	-0.7353	-0.7109	0.7051
	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Procedural Reaction Time	PRT Mean RT Correct Responses	PRT Median RT Correct Response	PRT Mean RT	PRT Median RT	PRT Throughput
	-0.7386	-0.7085	-0.7388	-0.7092	0.7098
	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Code Substitution	CS Mean RT Correct Responses	CS Median RT Correct Responses	CS Mean RT	CS Median RT	CS Throughput
	-0.7603	-0.7843	-0.7467	-0.7761	0.7251
	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001
	ACCURACY SENSITIVE				
Sternberg Memory Search	MS Number Correct	MS Percent Correct	MS Number Incorrect	MS Percent Incorrect	
	0.8122	0.8122	-0.8122	-0.8122	
	< 0.0001	< 0.0001	< 0.0001	< 0.0001	All Data Presented:
Spatial Processing	SP Number Correct	SP Percent Correct	SP Number Incorrect	SP Percent Incorrect	Parameter
	0.7897	0.7897	-0.7897	-0.7897	Pearson r
	< 0.0001	< 0.0001	< 0.0001	< 0.0001	P value (two-tailed)
Code Substitution	CS Number Correct	CS Percent Correct	CS Number Incorrect	CS Percent Incorrect	
	0.7711	0.7711	-0.7711	-0.7711	
	< 0.0001	< 0.0001	< 0.0001	< 0.0001	

Conclusion

The neurocognitive tests employed in the DANA mobile assessment were highly correlated with conventional MMSE measurements employed in the treatment of depressed patients undergoing ECT treatment. Results suggest that DANA is an effective tool for assessing cognition in patients with major depression.

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3. "Evaluation of the Cognitive and Behavioral Impact of ECT of Major Depressive Disorder," Submitted by Adam Kaplin, M.D., Johns Hopkins University, Baltimore, Maryland, in Support of Proposal, "Transitioning the Defense Automated Neurobehaviorial Assessment (DANA) to Operational Use," Submitted by Corinna Lathan, Ph.D., AnthroTronix, Inc., Silver Spring, Maryland, Proposal Number 12097007, Award Number W81XWH-12-C-0204, HRPO Log Number A-17665.1

Development of an Objective, Functional Biomarker of Invisible Wounds of War for Use by Providers

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The views contained in this poster are those of the authors, and not of the Department of Veterans Affairs and the Department of Defense

Abstract

Post deployment stress is marked by high rates of post-traumatic stress, depression, insomnia, and other mental health conditions that may go undiagnosed and therefore untreated. In the military, there is often under-reporting or over-reporting of symptoms indicative of mental or physical health problems associated with impaired performance. Assessments based on self-reported symptoms are not always effective in detecting underlying psychological conditions or problems. This study examined the potential for using computerized neurocognitive tests (CNTs) as an objective biomarker of functional impairment in a functioning, non-clinical, military population in order to complement subjective reporting of symptoms. Although, extensive neuropsychological testing can be performed for research purposes, this is often difficult in clinical practice as there are relatively few neuropsychologists; time and cost is often prohibitive, and traditional measures may only detect severe impairment. CNTs using precise speed and accuracy measures hold the promise of being more sensitive, as well as being more easily disseminated and utilized in a variety of healthcare settings. This research aimed to determine if neurocognitive functioning was associated with emotional and somatic distress in a sample of combat veterans. Differences for those with and without significant symptoms of PTSD, Depression, Insomnia, and Anger were compared across seven neurocognitive tests. Sensitivity and specificity of the tests were also determined. Medium to small effect sizes were found on cognitive performance for all psychological factors. Results suggest that the CNT provided a reliable and sensitive measure that has the potential for being utilized by clinicians for initial diagnosis, treatment disposition, and potentially assessing improvement and return to work determinations.

Introduction

Currently, there are no standardized, objective assessments or biomarkers available for predicting or determining diagnostic cut-offs for psychological conditions or problems such as PTSD, Depression, Insomnia, Anger, or post-concussive symptoms. CNT data was collected from active duty personnel using the Defense Automated Neurobehavioral Assessment (DANA). DANA is a CNT that was developed for the Department of Defense (DoD) as a clinical decision support tool for assessing neurobehavioral functioning both in-field and in-clinic. This research investigates the general assumption that various risk factors (PTSD, Depression, Insomnia, anger, pain, etc.) lead to significantly slower and less accurate (throughput) performance on cognitive tests. DANA's primary purpose is to assist providers in determining current level of cognitive functioning and to track recovery over time. This study analyzed DANA's ability to operate as an objective neurocognitive biomarker for cognitive impairment that is associated with PTSD, Depression, Insomnia, Anger, and post-concussive symptoms (3+ or 0-1). The study also determined the sensitivity and specificity of DANA neurocognitive measures to discriminate the accurate diagnosis for this population.

Question 1: Do CNT tests or composite scores correspond to diagnostic cut-offs for PTSD, Depression, Insomnia, Anger, or post-concussive symptoms for 0-1 or 3 or more concussions?

Question 2: Which CNT tests and composite scores are most closely associated with diagnostic cut-offs for PTSD, Depression, Insomnia, Anger, or post-concussive symptoms for 0-1 or 3 or more concussions?

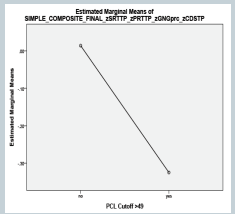
Methods

DANA Standard military version CNT was administered on hand-held devices to 646 active duty service members from the 2nd Marine Expeditionary Force. The battery included assessments for emotional distress (PCL-m, PHQ-8, anger); postconcussive symptoms (based on a revised NSI-22; insomnia (PSQI), and neurocognitive functioning (Simple Reaction Time – SRT; Procedural Reaction Time – PRT); Go-NoGo (GNG), Spatial Rotation Discrimination (SRD), Code Substitution Learning (CDS), Code Substitution Delayed (CDD), and Sternberg Running Memory (STN). Following IRB-approved consenting of participants, testing took about 40 minutes. Subjects were generally between the ages of 19-22, and were either Never Deployed, Previously Deployed (more than one year prior to testing), or Recently Deployed (within six months of testing). Throughput (TP) was calculated for each neurocognitive measure (number of correct responses in one minute). A Simple Composite Score based on four simple reaction time tests was calculated by averaging the z scores of SRT TP; PRT TP; GNG% and CDS [(zSRT TP + zPRT TP,+ zGNG% + zCDS) / 4]. A Complex Composite Score was the average of the z scores for the three more cognitively tasking tests SRD TP; CDD %; and STN% [(zSRD TP + zCDD % + zSTN%) / 3]. The Total Composite Score was the average of the two composite scores [(Simple + Complex) / 2]. Cut-offs and measures for each symptom were as follows: PTSD (PCL-m >49), Depression (PHQ-8 >10), Anger (DSI >1SD), and insomnia (PSQI>11).

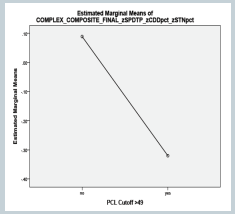
Results

General Linear Modeling was used for between-group ANOVA to compare groups above and below the diagnostic cut-off for each symptom. Generalized Linear Modeling (with Wald statistic and Robust Estimator) was utilized to confirm significance when groups were associated with unequal variances per Levene's test of homogeneity. Medium to small effect sizes were found on CNT performance for all psychological factors. Receiver Operating Characteristic (ROC) curve analyses was done to measure sensitivity and specificity of the measures for the different diagnostic cut-offs. See table and figures for details. The z score for SRT TP showed significant differences for all factors. The Simple Composite was more sensitive than the Complex Composite Score overall. Details of the findings are presented.

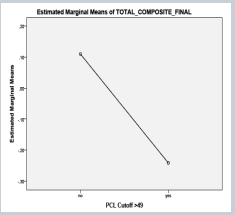
Simple Composite Score for **PTSD**
(F= 7.342, P=.007, η^2_p=.018)



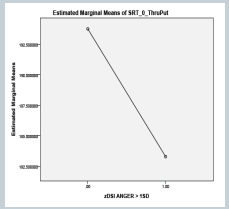
Complex Composite Score for **PTSD**
(F= 10.878, P=.001, η^2_p=.037)



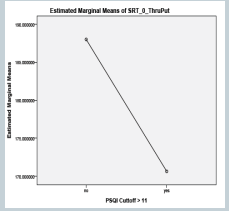
Total Composite Score for **PTSD**
(F= 10.190, P=.002, η^2_p=.036)



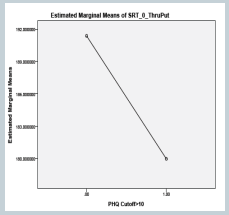
Simple Reaction Time Throughput for **ANGER** (F=11.795, P=.001, η^2_p=.018)



Simple Reaction Time Throughput for **INSOMNIA**
(F= 6.207, P=.013, η^2_p=.017)



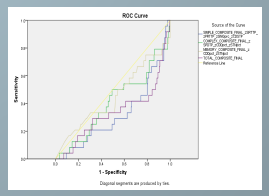
Simple Reaction Time Throughput for **DEPRESSION**
(F= 7.740, P=.006, η^2_p=.018) (Wald=5.458, DF=1, P=.019



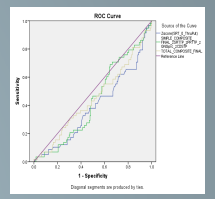
Sensivity and Specificity of zSRT_TP and Total Composite Scores

Diagnostic Cut-Off	Measure	Level	Sensitivity	Specificity
For 3 plus lifetime concussions	Total Composite	½ SD below mean	.70	.80
	Total Composite	1 SD below mean	.87	.93
For Insomnia (ISI>12)	zSRT_TP	½ SD below mean	.66	.84
(Total Composite Score was not predictive)	zSRT_TP	1 SD below mean	.79	.91
For PTSD (PCL>49)	Total Composite	½ SD below mean	.64	.90
	Total Composite	1 SD below mean	.92	.96
DEPRESSION (PHQ>10),	zSRT_TP	½ SD below mean	.63	.73
(Total Composite Score was not predictive)	zSRT_TP	1 SD below mean	.75	.86
For >MODERATELY HEAVY COMBAT EXPOSURE	zSRT_TP	½ SD below mean	.70	.83
(Total Composite Score was not predictive)	zSRT_TP	1 SD below mean	.82	.91
	zSRT_TP	½ SD below mean	.70	.83
	zSRT_TP	1 SD below mean	.82	.91
For Anger-Somatic (Neurobehavioral Symptom Inventory) > 1SD	zSRT_TP	½ SD below mean	.64	.77
(Total Composite Score was not predictive)	zSRT_TP	1 SD below mean	.77	.88
For Balance Symptoms (Neurobehavioral Symptom Inventory) > 1SD	zSRT_TP	½ SD below mean	.64	.74
(Total Composite Score was not predictive)	zSRT_TP	1 SD below mean	.80	.87

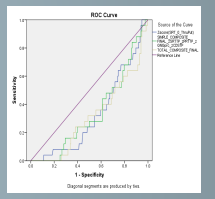
ROC curves for >3 lifetime concussions (Simple and Total Composite Scores were significant to <.01)



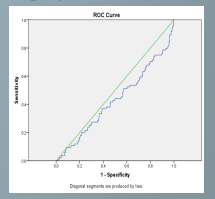
ROC curves for Insomnia (ISI >12) (zSRT_TP was significant to <.05)



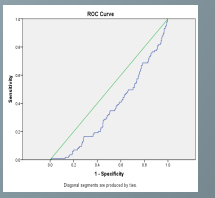
ROC curves for PTSD (PCL-M>49) (zSRT_TP, Simple, and Total significant to <.05)



ROC curves for Depression (PHQ-8 >10) (zSRT_TP significant to <.05)



ROC curves for Anger (NSI >1SD) (zSRT_TP significant to <.05)



Performance on the Defense Automated Neurobehavioral Assessment Battery (DANA) and simulated driving performance over 50h of continuous wakefulness: Correlation between Neurocognitive and Operational Performance (#2003).

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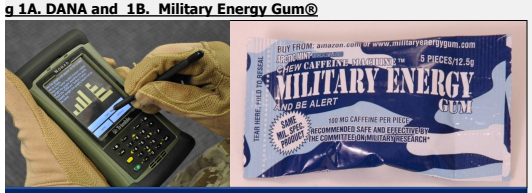
Background

Sleep deprivation and fatigue are major contributors to performance degradation in laboratory and operational settings[1-3]. In continuously operating work environments, performance decrements can have serious consequences. In fact, serious accidents and fatalities as a result of driving while sleepy are well documented[4]. Evaluating operational readiness requires understanding of available, relevant information with the means to detect and adjust for shortcomings. In studies of operational performance, additional, and often simple, tasks are also examined to assess neurocognitive performance. It can be generalized that some constructs measured by operational and neurocognitive tasks overlap, but the relationship and utility of using one to predict another under the condition of sleep deprivation has been lacking.

This study examined the relationship between neurocognitive and driving performance during 50h of sleep deprivation in subjects receiving caffeine or placebo. Performance over time was assessed and the relationships between performance metrics were sought in an effort to predict operational performance using a neurocognitive test.

g 1A. DANA and 1B. Military Energy Gum®



Methods

articipants

- Twenty-four healthy subjects (9 female) aged 18-31(22.5±2.9) yr, randomly assigned to caffeine (CAF, n=12) or placebo (PLA, n=12) groups.
- Low to moderate CAF users (<250mg CAF/day).
- Regular sleep wake patterns with an average total sleep time of 8.6±0.6h, verified with sleep diaries and activity monitors.

leasures

Defense Automated Neurobehavioral Assessment (DANA) – Rapid The DANA (Fig 1A) is a 5 min neurocognitive battery consisting of three subtasks: simple reaction time (SRT), procedural reaction time (PRT) and a go-no-go (GNG) task.

Primary variables were reaction time (RT), accuracy (ACC), Lapses (LAPS) and throughput (TP)

Driving Simulator – The driving task simulated a monotonous drive at dusk thru the Australian outback (little scenery, few road cues) and the requirement to maintain speed at 80 kph. Each 40 min test was completed on a full motion platform with audio ques.

Primary variables were speed maintenance (SM) lane deviations (LD) and crashes (CR).

esign/Procedure

Participants had baseline sleep (10h TIB, Day 1/2), followed by 50h of sleep deprivation (beginning Day 2 at 0800) and one daytime recovery sleep period (9h TIB, Day 5).

Participants chewed two pieces (100 mg CAF/piece) of Military Energy Gum® (Marketright Inc, Plano, IL, Fig 1B) or PLA at 0100, 0300, 0500, and 0700 on Days 3 & 4 during sleep deprivation.

Throughout the study participants completed a range of neurobehavioral tests every 4 h.

Between test periods participants refrained from physical activity (casual walking was allowed if participants were struggling to stay awake), but could do leisure activities (e.g., watch DVD's, play board/card games, etc.) in a shared lounge area.

Statistical Analyses

Mixed-model analysis (3-way) was used to analyze between group differences and change over time for DANA and driving performance (DRP). Fixed effects included group (CAF, PLA), gender, and time (15 test periods) with a random effect for subjects. Between-subject correlations (Pearson product-moment) were used to assess the relationship between average DANA and DRP variables over time by correlating mean performance variables (by group) at each of the 15 test periods. CAF & PLA correlations that were largest and similar in magnitude were used to identify the DANA metric that had the strongest relationship with driving performance (DANA RT, LAPS & TP; DRP LD & CR). Within-subject correlations (Pearson product-moment) were calculated for each individual over time to assess DANA and associated DRP change within each individual and within-subject correlations were summarized by direction and significance. A 'common' within-subject correlation for each group was calculated using analysis of covariance; largest PLA correlations were used to identify the strongest DANA and driving performance relationship. Lapse and crash data were analyzed after applying a Log10(x+1) transformation. Statistical significance was set at p = 0.05.

Results

- There were significant declines in all DANA subtask metrics and DRP metrics (time [p < .0001] and group x time interaction [p <.001]).
- Significant differences from baseline in DANA and DRP were observed at similar times (0300-0600, Day3) for PLA for all performance measures (Fig 2B, 3B).
- CAF performance declined with an increase in LD and SRT TP after 0300 Day4 (Fig 2A) while performance was maintained in CR and SRT LAPS (Fig 3A).
- Correlations for 24 pairs of DANA and DRP data were analyzed for each group.
- All CAF and PLA between-subject correlations were significant.
- Strongest between-subject correlations (Table 1): LD and SRT TP (Fig 4A); CR and SRT LAPS (Fig 4B).
- Within-subject correlations showed directional coherence in 82% - 100% of subjects and 35% - 75% were significant.
- All CAF and PLA common within-subject correlations were significant except CAF CR and PRT LAPS correlation.
- Strongest within-subject correlations: LD and SRT TP ($r_{caffeine}$ = -.60, p<.0001; $r_{placebo}$ = -.71, p<.0001); CR and PRT TP ($r_{caffeine}$ = -.32, p<.0001; $r_{placebo}$ = -.64, p<.0001).

Fig 2. Group Means Over Time in Lane Deviations and SRT Throughput for CAF (A) and PLA (B). Red arrows indicate CAF/PLA administration times.

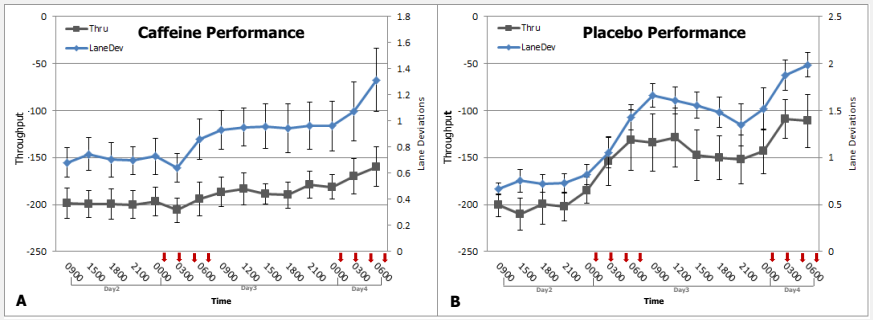


Fig 3. Group Means Over Time in Crashes and SRT Lapses for CAF (A) and PLA (B). Red arrows indicate CAF/PLA administration times.

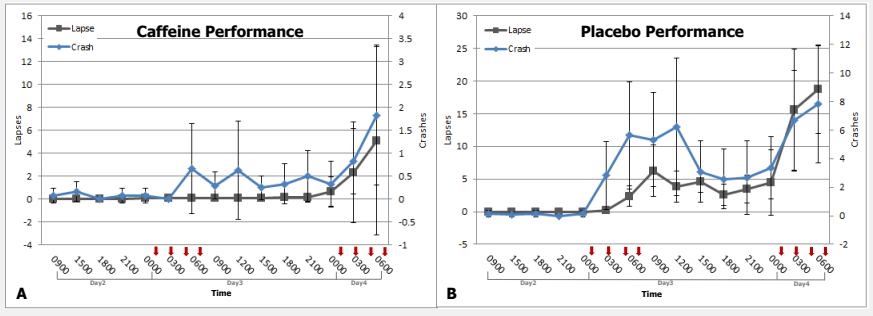


Fig 4. Between-subject correlation plots for Lane Deviations and SRT Throughput (A) and Crashes and SRT Lapses (B). Red circles are mean CAF performance and blue squares are mean PLA performance.

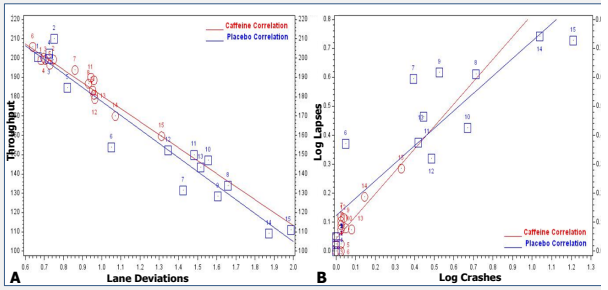


Table 1. Strongest between-subject (and corresponding within-subject) correlations for Driving and DANA performance in CAF and PLA groups.
Additional correlations between DP and DANA metric are available upon request. *p<.05

	Lane Deviations & SRT Throughput		Crashes & SRT Lapses	
	Between-subject	Within-subject	Between-subject	Within-subject
Caffeine	-0.97*	-0.60*	0.88*	0.21*
Placebo	-0.96*	-0.71*	0.89*	0.59*

Summary

- The onset of DANA and driving performance decrements appeared to be similarly impacted by sleep deprivation after 0300 (20 hr awake) in the placebo group and end of the study in the caffeine group.
- The strength of the between-subject correlations demonstrate that the DANA can be used as an indicator of average driving (i.e., operational) performance.
- DANA SRT had the strongest relationships with driving measures in both groups.
- Lane deviations had the strongest between- and within-subject correlations with SRT throughput: decreases in throughput (correct responses rate with respect to reaction time) was related to increases in driver swerving.
- Crashes had the strongest between-subject relationship with SRT lapses: as the number of lapses increased, so did the average number of crashes. Within-subject correlations for crashes had a stronger relationship with PRT throughput.
- The magnitude and directional coherence of within-subject correlations support that DANA and driving performance relationships hold true for an individual.
- Within-subject correlations were not as strong as between-subject correlations most likely a result of interindividual difference (e.g. sensitivity/insensitivity to caffeine/sleep loss, etc.).
- Caffeine within-subject correlations with crashes were low because the majority of subjects given caffeine did not crash.
- Overall, the consistency, magnitude, and statistical significance of between- and within-subject correlations demonstrates the aptitude of DANA's ability to predict driving performance (average and individual) during sleep deprivation.

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Differences in Cognitive Efficiency in Active Duty Military – Healthy vs. Those With Sleep Disturbance, Depression, and/or PTSD Using The DANA Automated Neurocognitive Assessment (DANA) Tool

Corinna Lathan, Angela S. Wallace, and Rita Shewbridge
AnthroTronix, Inc.

Introduction

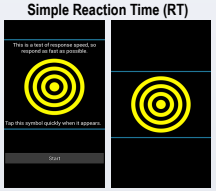
Neurocognitive assessment tools (NCATs) are key to assessing neurocognitive function quickly and effectively in operational environments. The Defense Automated Neurobehavioral Assessment (DANA) is a portable FDA-cleared NCAT. DANA has demonstrated excellent reliability in a variety of military field conditions.

Methods

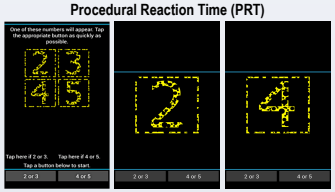
Data Collection: DANA was administered to 806 active-duty military (71% Male) ages 18 to 64.

Measures: *Simple Reaction Time (RT)* – Participant taps location of yellow target as quickly as possible each time it appears. *Procedural Reaction Time (PRT)* – Screen displays one of four numbers for three seconds. Subject presses on left button ("2" or "3") or right button ("3" or "4") depending on number presented. *Code Substitution Learning (CSL)* – Subject refers to a code of 9 symbol-digit pairs shown across the upper portion of the screen. A sequence of single symbol-digit pairs is shown below the key. Subject indicates whether or not the single pair matches the code by pressing "Yes" or "No". *Go/No-Go (GNG)* – A house is presented on screen with several windows. Either a "friend" (green) or "foe" (white) appears in a window. Subject must push a "fire" button only when "foe" appears.

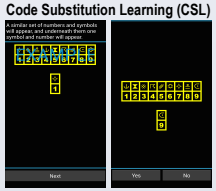
Simple Reaction Time (RT)



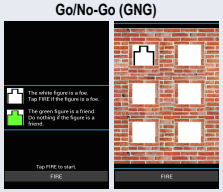
Procedural Reaction Time (PRT)



Code Substitution Learning (CSL)



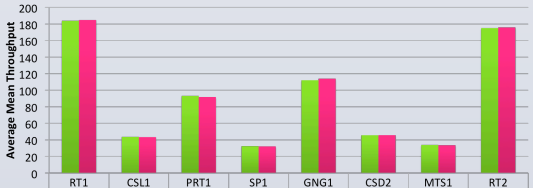
Go/No-Go (GNG)



Data Analysis: *T*-tests comparing mean throughput (a measure of cognitive efficiency; Thorne, 2006) on AM and PM administrations and mean throughput between self-reported healthy and "unhealthy" participants (i.e. reported symptoms related to sleep disturbances [PSQI ≥ 7], depression [PHQ8 ≥ 10], and/or PTSD [PCLM ≥ 30]) was conducted.

Results: Diurnal Analysis

AM vs. PM Administrations



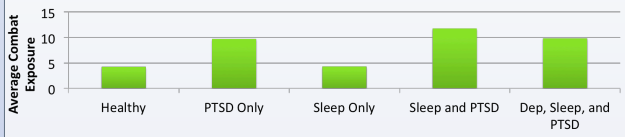
	RT1	CSL1	PRT1	SP1	GNG1	CSD2	MTS1	RT2
AM	184.0	43.7	93.2	32.4	112.1	45.6	33.9	175.1
PM	184.9	43.4	91.8	32.2	114.0	45.7	33.6	176.0

N_{AM} = 360-424 N_{PM} = 350-406. *p < .05, **p < .01, ***p < .001.

No significant differences in mean throughput between AM and PM for any DANA subtests.

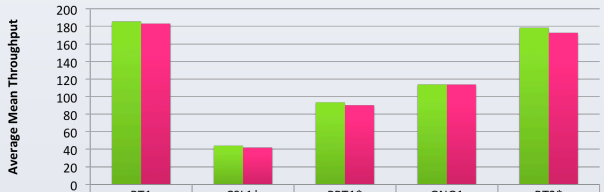
Results: Optimal Well-Being versus Compromised Well-Being by Condition

Combat Exposure



Differences in Combat Exposure: Healthy participants had the least amount of combat exposure (M = 4.25) followed closely by participants with disturbed sleep (M = 4.30). The level of combat exposure experienced by these two groups is considered "light combat" (Keane et al., 1989). Participants who reported PTSD experienced "light to moderate combat" exposure. Of those in groups reporting PTSD, participants with only PTSD had the least combat exposure (M = 9.71) followed by those with depression, disturbed sleep, and PTSD (M = 9.83). Finally, participants with disturbed sleep and PTSD had the most combat exposure (M = 11.77).

Healthy vs. PTSD ONLY

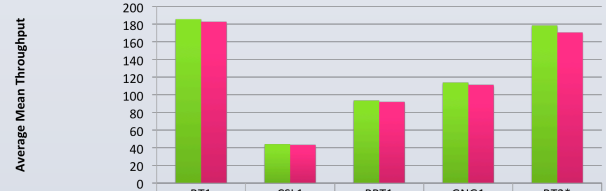


	RT1	CSL1†	PRT1*	GNG1	RT2*
Healthy	185.7	44.1	93.5	113.9	178.6
PTSD ONLY	183.3	41.9	90.3	113.8	172.8

$N_{Healthy}$ = 521-552, $N_{PTSD\ ONLY}$ = 66-67. *p < .05, **p < .01, ***p < .001.

Healthy participants have significantly higher PRT1 and RT2 mean throughput than participants with PTSD.

Healthy vs. Sleep Disturbed ONLY



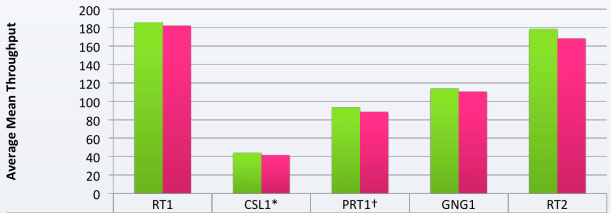
	RT1	CSL1	PRT1	GNG1	RT2*
Healthy	185.7	44.1	93.5	113.9	178.6
Sleep Disturbed ONLY	182.7	43.3	92.0	111.3	170.6

$N_{Healthy}$ = 521-552, $N_{Sleep\ Disturbed\ ONLY}$ = 95-102. *p < .05, **p < .01, ***p < .001.

Healthy participants have significantly higher RT2 mean throughput than sleep disturbed participants.

Results: Optimal Well-Being versus Compromised Well-Being by Condition (cont'd)

Healthy vs. Sleep Disturbed and PTSD

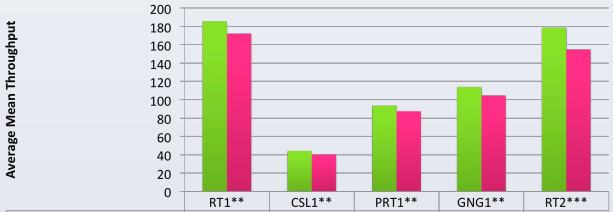


	RT1	CSL1*	PRT1†	GNG1	RT2
Healthy	185.7	44.1	93.5	113.9	178.6
Sleep and PTSD	182.2	41.7	88.6	110.5	168.3

$N_{Healthy}$ = 521-552, $N_{Sleep\ and\ PTSD}$ = 36-37. *p < .05, **p < .01, ***p < .001.

Healthy participants have significantly higher CSL1 mean throughput than participants with disturbed sleep and PTSD.

Healthy vs. Sleep Disturbed, Depressed, and PTSD



	RT1**	CSL1**	PRT1**	GNG1**	RT2***
Healthy	185.7	44.1	93.5	113.9	178.6
Sleep, Depressed, and PTSD	172.1	40.3	87.4	104.6	154.8

$N_{Healthy}$ = 521-552, $N_{Sleep,\ Depressed,\ and\ PTSD\ ONLY}$ = 36-41. *p < .05, **p < .01, ***p < .001.

Healthy participants have significantly higher mean throughput on RT1, RT2, CSL1, PRT1, and GNG1 than participants with all three conditions combined.

Conclusions

First, DANA provides stable assessments of mean throughput regardless of the time of day DANA is administered. Second, active duty military who report being depressed, having disturbed sleep, and/or PTSD have worse cognitive performance on reaction time, simple executive functioning, attention, and speed and accuracy of targets than active military who do not report any of the aforementioned conditions. Lower cognitive efficiency can have potentially harmful effects to individuals and to others with whom these individuals interact with to complete various activities while in the field (e.g. responding to a target in time to thwart an attack). DANA can aid in identifying decreases in cognitive efficiency in the field.

References

Keane, T. M., Fairbank, J. A., Caddell, J. M., Zimering, R. T., Taylor, K. L., & Mora, C. A. (1989). Clinical evaluation of a measure to assess combat exposure. *Psychological Assessment, 1*, 53-55.

Thorne, D. R. (2006). Throughput: A simple performance index with desirable characteristics. *Behavior Research Methods, 38*, 569-573.

Contact Information

Corinna (Cori) Lathan, cori.lathan@atinc.com

Appendix K

Title: Longitudinal evaluation using the recently developed Defense Automated Neurobehavioral Assessment (DANA) tool of the cognitive impact of Electroconvulsive Therapy (ECT) in the treatment of Major Depressive Disorder (MDD)

Steven Royce Woods MD MEd[1], Ryoko Susukida PhD[3], Alison Riehm BS[1], Henry Askew, Kristen Rahn PhD[1,2], Corinna Lathan PhD[4], Adam Kaplin MD PhD[1,2]

Departments of Psychiatry[1] and Neurology[2], Johns Hopkins University School of Medicine, Baltimore, MD, USA; Department of Mental Health[3], Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA; AnthroTronix[4], Silver Spring MD

Major Depressive Disorder (MDD) has been a major source of morbidity and mortality, and is often associated with cognitive impairment. Little is understood about the cognitive effects of electroconvulsive therapy (ECT) during the treatment course among patients with MDD. Our study represents a novel, automated assessment of the effect on cognitive functioning of patients receiving ECT treatment for MDD. The objectives of this study were to measure cognitive changes in MDD patients during their course of ECT treatment. We also correlated cognitive measures obtained by administering DANA with results of mini mental status examinations (MMSE). DANA is a new neurocognitive assessment tool that includes a library of standardized cognitive and psychological assessments. A neurocognitive and psychological assessment battery was conducted on an electronic tablet with DANA software, throughout the course of ECT treatment. Results of DANA assessments were then correlated with standardized MMSE results employed for clinical purposes. Preliminary analyses of pilot data indicate that DANA performance correlated with MMSE in the majority of outcomes. The correlation between MMSE and aspects of the following tests gave an absolute correlation coefficient $r > 0.7$, with $p<0.0001$: Code Substitution, Spatial Processing, Procedural Reaction and Simple Reaction Time. Correlation between MMSE and aspects of the Sternberg Memory Search gave an even higher absolute correlation coefficient $r > 0.8$, $p<0.0001$. The neurocognitive tests employed in the DANA mobile assessment were highly correlated with conventional MMSE measurements employed in the treatment of depressed patients undergoing ECT treatment. Results suggest that DANA is an effective tool for assessing cognition in patients with major depression.

Biography

Dr. Woods completed his MD at Howard University College of Medicine in Washington DC. He began his postdoctoral research experience at the Center for Autism and Related Disorders (CARD) at the Kennedy Krieger Institute in Baltimore MD, after which he completed 2 years of general pediatrics residency at the Children's Hospital of Michigan in Detroit MI. He returned to Baltimore MD to continue his postdoctoral research at John's Hopkins University School of Medicine in his current role as an e-health and psychiatry postdoctoral research fellow in the Department of Psychiatry and Behavioral Sciences. His research interests include studying cognition among patients with major depression, the use of technology to improve patient care, suicide prevention, and risk reduction among vulnerable groups.

Outline

Background

Feasibility and Reliability Data

Validity and Utility – Cross-Sectional Data

Longitudinal Validity – Sensitivity to Impairment over time

Clinical Studies

History of DANA

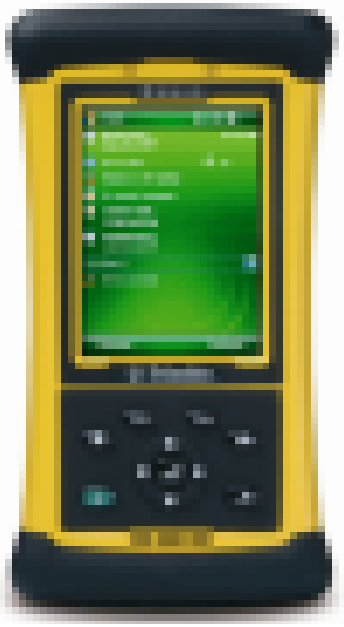
- Developed for the Department of Navy Bureau of Medicine and Surgery (BUMED) in response to RFQ
- A mobile software application to assist in the detection of neurocognitive impairment from any cause
  - Concussion
  - Combat-related psychological distress
  - Deployment-related exhaustion
- To help the far forward medic to more accurately detect impairment as soon as possible
- To assist the psychologist or healthcare professional with supportive diagnostic tools to aid in their diagnosis

DANA Requirements

- Portability
- State of the art NeuroCognitive Assessment Tool (NCAT)
  – Build on Best Practices
- Both standardized cognitive and psychological tests
- Embedded tests of effort determine malingering vs real
- Easy of use for all types of providers – 3 levels of testing
- FDA Compliance
- Non-Proprietary

Platform

- Android OS (Beta iOS)
- Java Implementation
- Stylus or Touch Screen



DANA Tests

DANA Rapid

- within 24 hours following concussion
- to support corpsman's/medic's disposition

DANA Brief

- follow up to concussion assessment (after 24 hours)
- or when the Medic suspects impairment from any cause (concussion, emotional trauma, fatigue)

•DANA Standard

- for use by MO, BH, or allied healthcare professional to support diagnosis and disposition
- to assist in report writing and EMR

DANA Test Batteries

DANA Rapid (5 minutes)	DANA Brief (15 minutes)	DANA Standard (45 minutes)
Simple Reaction Time	Simple Reaction Time	Simple Reaction Time
Procedural Reaction Time	Code Substitution (Learning)	Code Substitution (Learning)
Go/No-Go	Procedural Reaction Time	Procedural Reaction Time
Optional: Combat MACE interview (additional 10 minutes)	Spatial Processing	Spatial Processing
	Go/No-Go	Go/No-Go
	Code Substitution (Recall)	Code Substitution (Recall)
	Simple Reaction Time	Matching to Sample
	Patient Health Questionnaire (PHQ-9)	Sternberg Memory Search
	Primary Care-PTSD Screen (PC-PTSD)	Simple Reaction Time
	Insomnia Severity Index (ISI)	Combat Exposure Scale (CES)
		Patient Health Questionnaire (PHQ-9)
		Pittsburg Sleep Quality Index (PSQI)
		PTSD Check List-Military Version (PCL-m
		Deployment Stress Inventory (DSI)

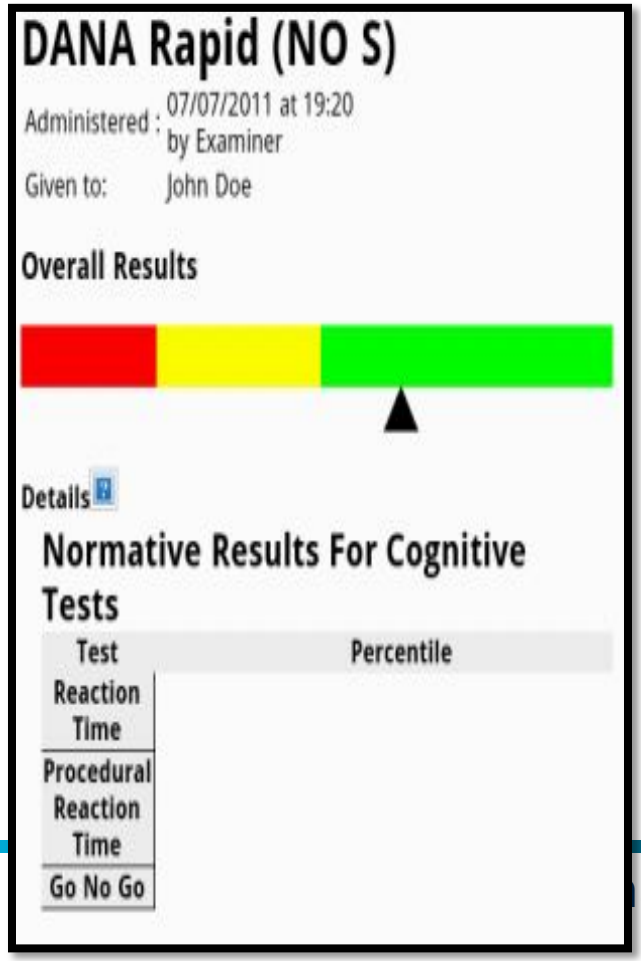
Output Screens

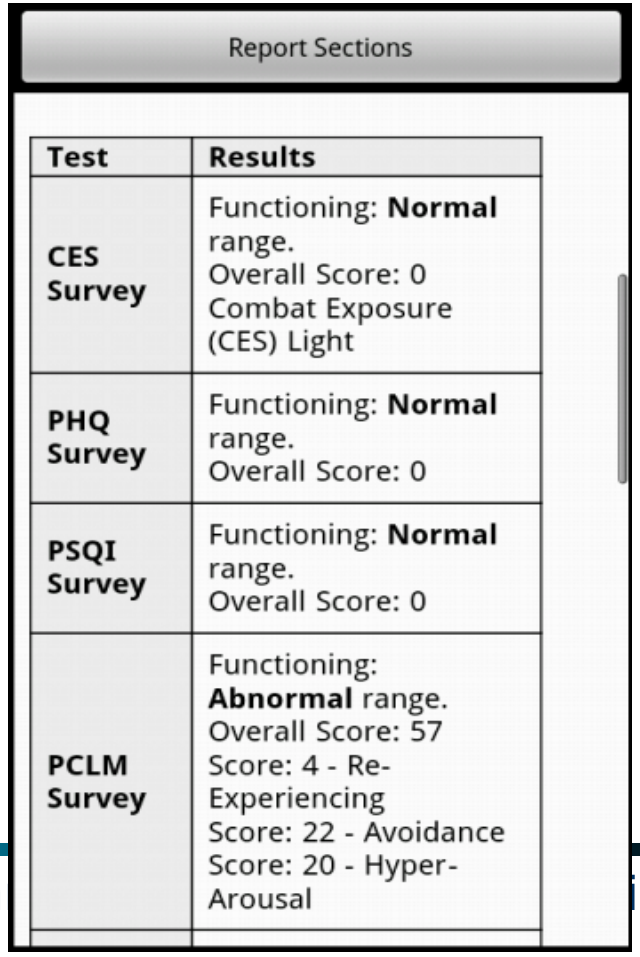
Tailored for use by a range of provider types

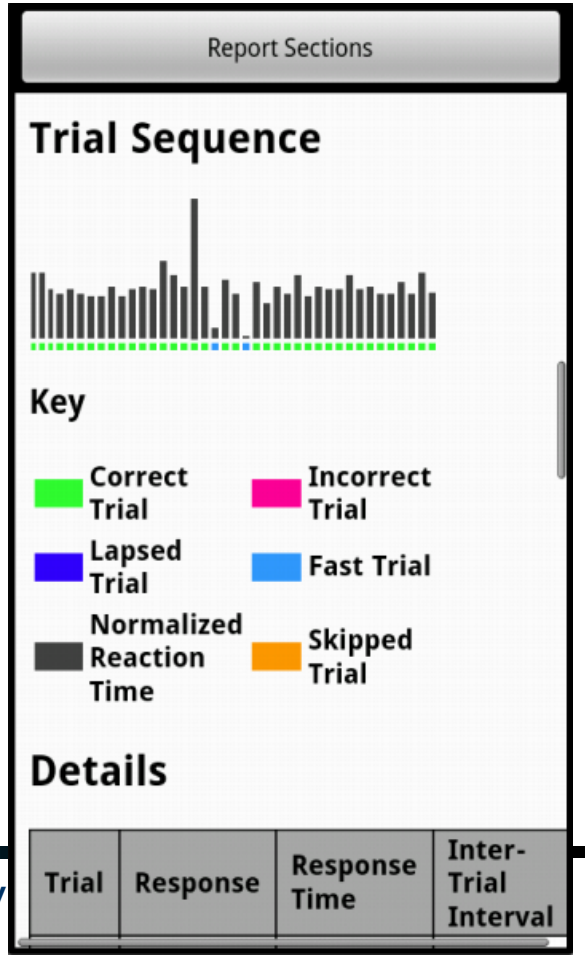
Medic

MO/BH

Neuropsychologist
Neurologist







FDA Regulatory Process

- July 2011 - Draft Guidelines for Mobile Medical Applications (MMA)
- April 2013 - Filed 513(g) for FDA device classification
- September 2013 - Met with FDA
- September 2013 - Final MMA Guidelines
- March 2014 - Received 513(g) response
- Implemented Quality System processes per FDA 21 CFR Part 820
- July 2014 - Filed 510(k) for premarket notification and authorization
- October 2014 FDA Clearance Received

FDA Cleared IFU

DANA provides clinicians with objective measurements of reaction time (speed and accuracy) to aid in the assessment of an individual's medical or psychological state.

Factors that may affect the measurement of reaction time include, but are not limited to concussion, head injury, insomnia, post traumatic stress disorder (PTSD), depression, attention deficit hyperactivity disorder (ADHD), memory impairment, dementia, delirium, prescription and non-prescription medication, some nutritional supplements, as well as a variety of psychological states (e.g. fatigue and stress).

DANA also delivers and scores standardized psychological questionnaires. DANA results should be interpreted only by qualified professionals.

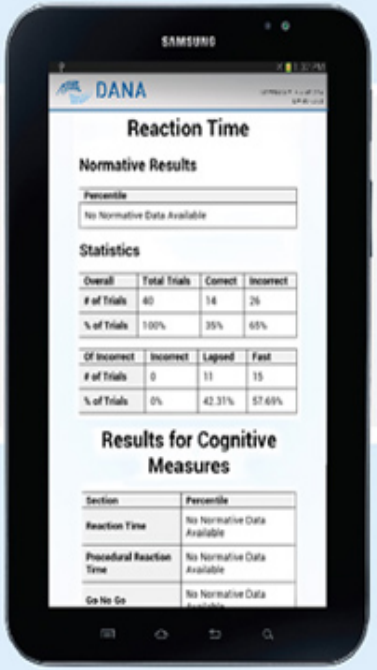
Scaleable Software

Brain Health Screening with DANA™ Software

FAST
Results in 5 minutes

COMPLETE
Full Spectrum of Tests from 5-Minute Rapid to 15-Minute Brief and 45-Minute Standard Testing Protocols

ACCURATE
Complements patient feedback with objective tests of cognitive efficiency and self-administered questionnaires



DANA Rapid – 5 Minutes
Within 24 hours of symptom onset. Measures cognitive function / brain vital signs.

DANA Brief – 15 Minutes
Follow-up to initial symptom assessment (after 24 Hours) For use when impairment of cognitive function is suspected.

DANA Standard – 45 Minutes
For use by physician or psychologist. Assists with reports and EMHR.

DANA Publications

Lathan, C., Spira, J. L., Bleiberg, J., Vice, J., & Tsao, J. W. (2013). ***Defense Automated Neurobehavioral Assessment (DANA)—Psychometric properties of a new field-deployable neurocognitive assessment too****l. Military Medicine 178(4): 365-71. doi: 10.7205/MILMED-D-12-00438*

Spira, J. L., Lathan, C. E., Bleiberg, J., & Tsao, J. W. (2014). **The impact of multiple concussions on emotional distress, postconcussive symptoms, and neurocognitive functioning, in active duty U.S. Marines independent of combat exposure or emotional distress**. *31:1-12 Journal of NeuroTrauma.*

Roach, E. B., Bleiberg, J., Lathan, C. E., Wolpert, L., Tsao, J. W., & Roach, R. C. (2014). ***AltitudeOmics: decreased reaction time after high altitude cognitive testing is a sensitive metric of hypoxic impairment****. NeuroReport [EPub], April 9, 2014.*

Subudhi AW, Bourdillon N, Bucher J, Davis C, Elliott JE, et al. (2014) ***AltitudeOmics: The Integrative Physiology of Human Acclimatization to Hypobaric Hypoxia and Its Retention upon Reascent****. PLoS ONE 9(3): e92191. doi:10.1371/ journal.pone.0092191*

NeuroReport

Russo, C, Wolpert, L, Lathan, C. (2015). **Test-retest reliability of the Defense Automated Neurobehavioral Assessment tool (DANA) as administered to a homogeneous population of healthy collegiate athletes**. *Applied Psych. Measurement, p. 1-7.*

Spira, JL, Haran, FJ, Flores, E, Tsao, J (2014). ***The relationship between the Automated Neuropsychological Assessment Metrics (ANAM) and Defense Automated Neurobehavioral Assessment (DANA) neurocognitive tests in a sample of US Marines*****.** *Manuscript in preparation.*

MHSRS 2014 –Presentations

King L, Spira J. Development of an objective, functional biomarker of invisible wounds of war for use by providers. Poster to appear at: Military Health System Research Symposium. 2014 Aug 18-21; Fort Lauderdale, FL.

King L, Spira J. Is simple reaction time the best indicator of white matter disruption in service members with invisible wounds of war? Presentation to appear at: Military Health System Research Symposium. 2014 Aug 18-21; Fort Lauderdale, FL.

Kaplin A, Woods S. Longitudinal evaluation using the recently developed Defense Automated Neurobehavioral Assessment (DANA) tool of the cognitive impact of Electroconvulsive Therapy (ECT) in the treatment of Major Depressive Disorder (MDD). Poster session to appear at: Military Health System Research Symposium. 2014 Aug 18-21; Fort Lauderdale, FL.

Eonta S, Kamimori G. Impact of caffeine on neurocognitive performance during sleep deprivation using the Defense Automated Neurobehavioral Assessment (DANA). Poster to appear at: Military Health System Research Symposium. 2014 Aug 18-21; Fort Lauderdale, FL.

Outline

Background

Feasibility and Reliability Data

Validity and Utility – Cross-Sectional Data

Longitudinal Validity – Sensitivity to Impairment over time

Clinical Studies

Psychometric Properties of DANA (MilMed 2014)

Five extreme deployable settings for durability and technical validation (n=240, >40/site)

- Shipboard (Yokosuka, heavy seas)
- Arctic (Greenland, winter)
- Desert (29 Palms, summer)
- Mountainous (Bridgeport)
- Jungle (Okinawa Humid Summer)

Outcomes

Robustness of technology – adequate session completion and data collection

User experience/interface feedback

Acquired distributions of data for power estimates for subsequent clinical data collection (total combined population, assessed by environment, age, and gender)

Reliability Measures

- Test-Retest Reliability is adequate (>.64 across all environments)
- Split-Half, Odd-Even Reliability (.76-.95)
- Compares favorably to ANAM on similar tests:
  - DANA-ANAM comparison(N=40): DANA had superior test-retest *r*
  - 3 largest ANAM samples published: DANA had similar mean/SD ratios

Longitudinal stability and reliability
(Applied. Psychol. Measurement, 2015)

Test-retest reliability of the DANA Rapid test battery, as administered to a homogeneous population of US Air Force Academy football team players before the commencement of the season, during the season, and following the end of the season.

- No significant differences in Throughput (TP) between testing sessions pre- and mid season, and between mid and post-season ($p>0.05$), per subtest.
- DANA is stable across the time scales of test and retest administrations.

Comparison to IMPACT and ANAM

DANA's ICC correlation coefficient (R) of 0.81 for Reaction Time (RT) exceeds that of both ANAM4 (0.60) and ImPACT (0.53) and DANA's ICC of 0.75 for Procedural Reaction Time (PRT) exceeds that of ANAM4 (0.51).

Battery	Subtest	<TP> T1	T2	SD < TP > T1	T2	N	**ICC (R)** LB	UB
DANA	PRT	102.9	106.8	13.02	12.57	89	**0.75** 0.60	0.84
	RT	192.4	198.3	26.77	23.54	87	**0.81** 0.69	0.87
ANAM4	PRT	97.62 103.56		13.10	10.31	50	**0.51** 0.28	0.69
	RT	86.88	91.38	11.46	12.76	50	**0.60** 0.39	0.75
ImPACT	RT	0.60	0.61	0.08	0.09	44	**0.53** 0.28	0.71

Active-duty military, aged 18-64, provides a relevant range of subjects by which a normative reference base can be used for the purpose of neurocognitive test comparison when baseline information is unavailable.

- Testing session consists of:
  - DANA Standard Test
  - Psychological screening questionnaires
  - Demographics
  - Survey of concussion history

- N > 800 subjects
- Data collection is ongoing

Establishing a Normative Data Sample in a Military Population
Ft. Hood Military Base

Age Bins by Gender

Bin	18-19	20-24	25-29	30-34	35-44	45-54	55-64
M	101	100	100	98	92	58	29
F	23	93	52	29	23	13	3

Psychological Characteristics of the Population

PTSD	None	82%
	Mild to moderate	15%
	Severe	3%
Depression	None	94%
	Mild to moderate	4%
	Severe	2%
Insomnia	None	73%
	Mild to moderate	23%
	Severe	4%

Outline

Background

Feasibility and Reliability Data

Validity and Utility – Cross-Sectional Data

Longitudinal Validity – Sensitivity to Impairment over time

Clinical Studies

Cross-Sectional Comparisons

Can an NCAT detect invisible wounds of war in Service Members returning from combat deployment?

How does Cognitive Testing (Throughput scores) relate to Concussion; PTSD; Depression; anger, pain, Insomnia; Postconcussive Sx, deployment?

Methods

N = 646 USMC 2MEF

Deployment:

- Never - Prior (>6 mo) - Recent (<6 mo)

Concussions (self-report):

- Recency (<6 mo) - Lifetime number

Cognitive Measures

- DANA Standard (435)
- DANA Rapid (646)

Psychological Factors (meeting criteria for):

- PTSD
- Depression
- Insomnia
- PsychoPhysical Sx
- CES

Results (J. Neurotrauma 2014)

Neurocognitive tasks were positive for distinguishing between those who met criteria for PTSD, depression, insomnia, anger, pain, and postconcussive symptoms (NSI-22). (via ANOVA, and Sensitivity/Specificity analyses (Moderate-Large effect sizes)

Cognitive tests could distinguish those who had been previously concussed, but only in those who had three or more lifetime concussions, even when accounting for independent covariates of PTSD, Depression, deployment, or combat experiences.

Only simple tests (SRT, PRT, GNG, CDS) were significant for detecting differences between normal and affected groups

- suggesting that white matter functioning is being tapped into, rather than higher cognitive factors.

Outline

Background

Feasibility and Reliability Data

Validity and Utility – Cross-Sectional Data

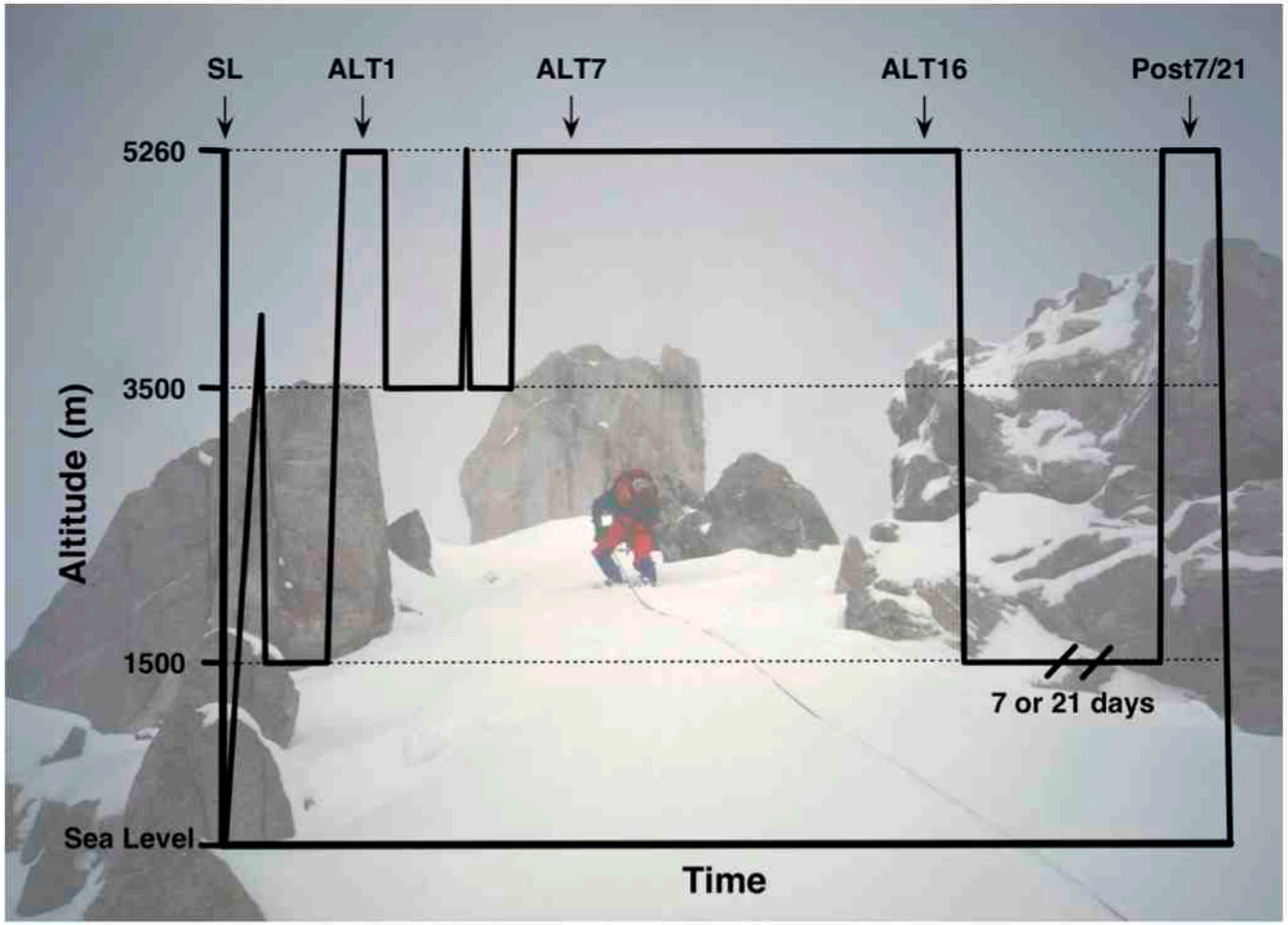
Longitudinal Validity – Sensitivity to Impairment over time

- **High Altitude Hypoxia**
- **In-Theatre Concussion**

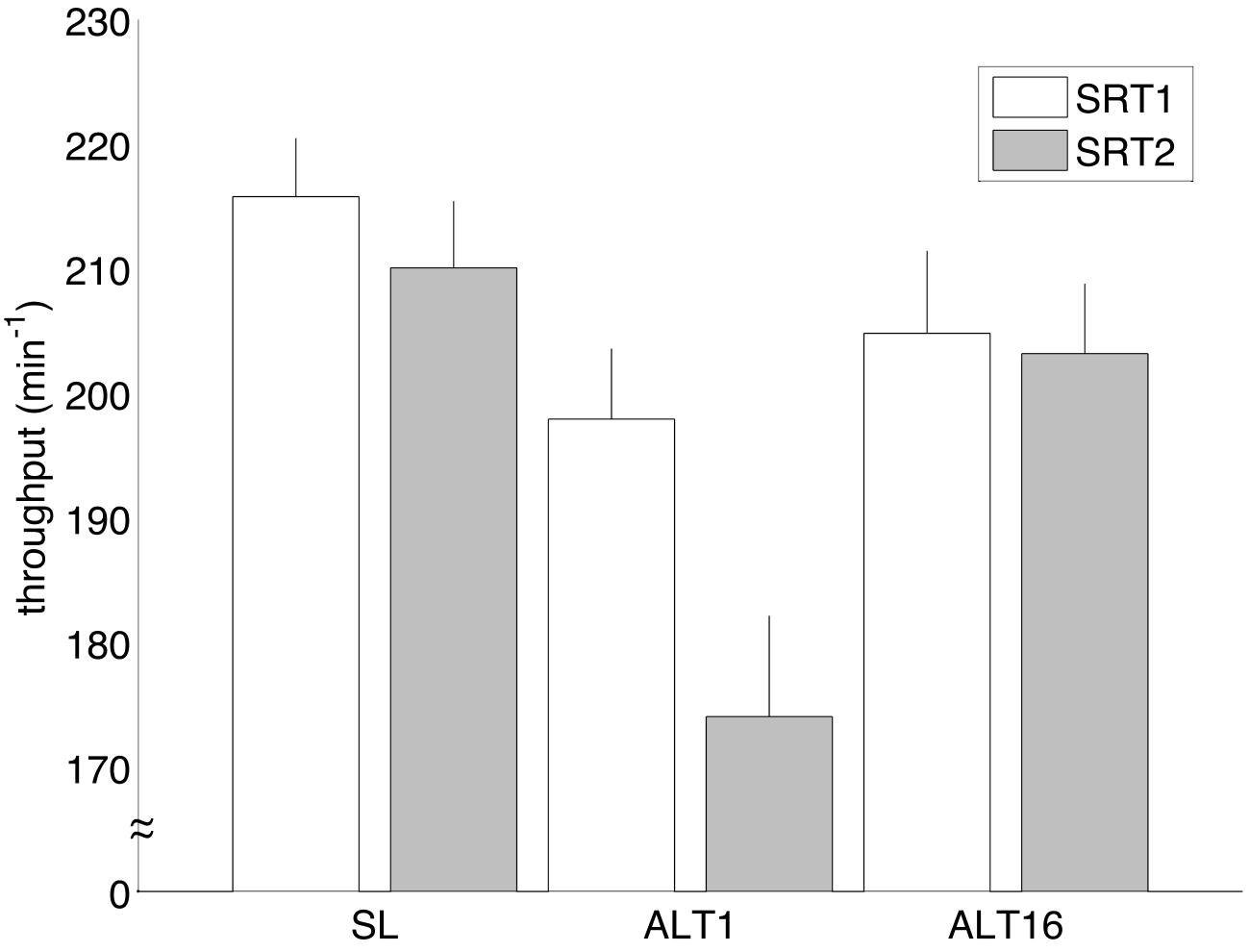
Clinical Studies

High Altitude Cognitive Testing

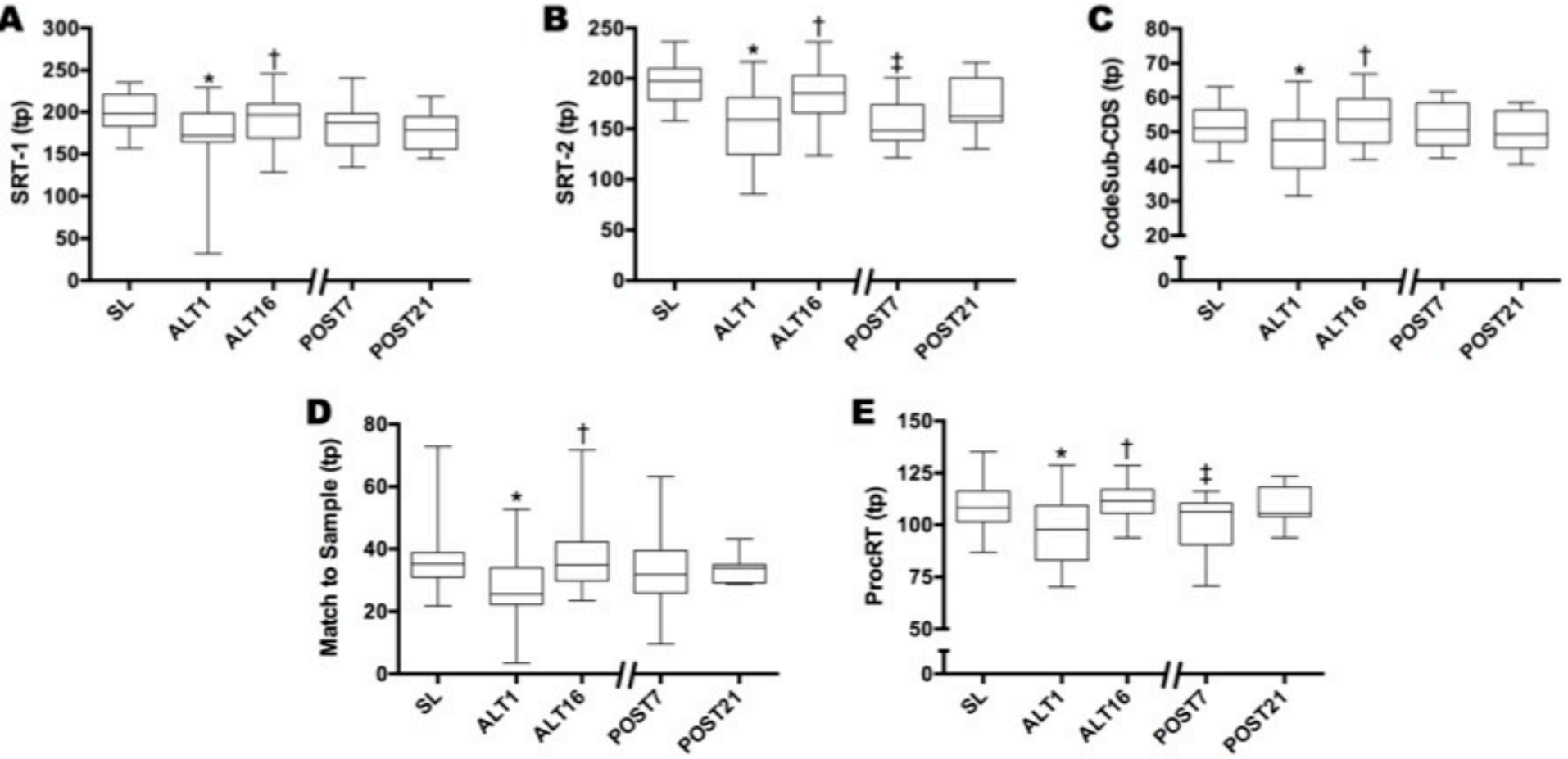
21 subjects (12 males, nine females, average age 20.8 yrs, range 19-23 yrs)



Decreased reaction time after high altitude cognitive testing is a sensitive metric of hypoxic impairment



Neurocognitive Function During Acclimatization and Upon Reascent



Human Inspired. Technology Driven.

In-Theater Concussion Assessment
Camp Leatherneck, Afghanistan

Cognitive testing with DANA and ANAM was simultaneously administered to both service members diagnosed with mild concussion (n~17) and to non-concussed service members (N~17).

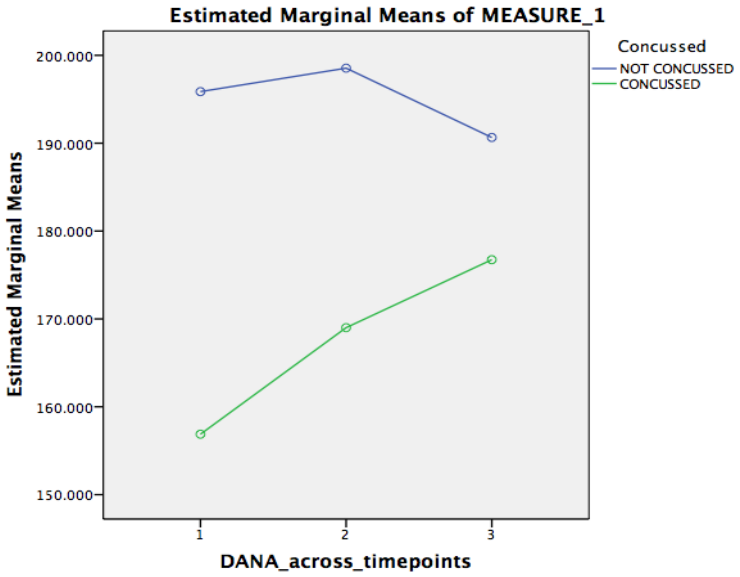
- Testing occurred within 3 days post-injury (or post-baseline for controls), and again 5 days post-injury.

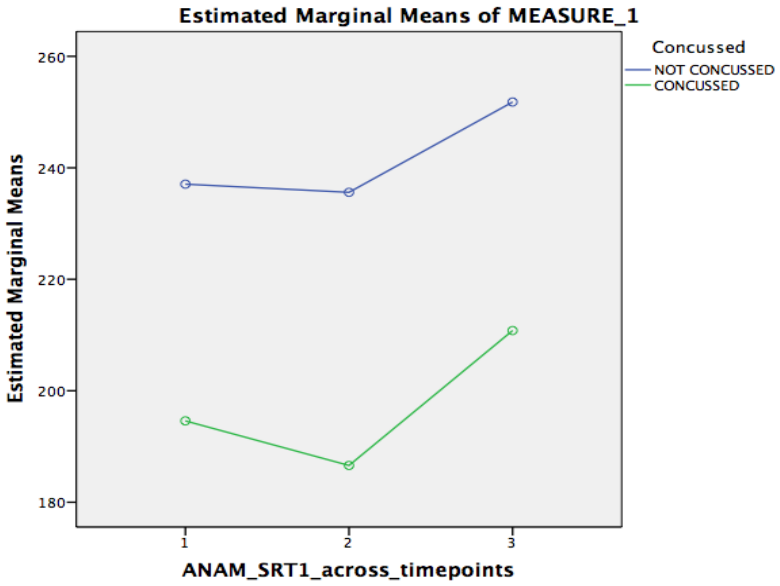
Results (note that it is a small n and may not be generalizable)

- **DANA and ANAM** For equivalent tests, DANA and ANAM have equivalent sensitivity (.93) to concussion and recovery. However DANA seems to have a higher specificity (.89), the ability to reject false concussion, than ANAM (.44)
- **DANA and MACE (n=40)** DANA shows concurrent validity against MACE in that DANA memory tests correspond to MACE recall tasks.
- **DANA Psychological Assessment** Symptomatic insomnia, depression, and PTSD are all observed to greater effect in concussed patients than in non-concussed patients.

In-Theater Concussion Assessment
Camp Leatherneck, Afghanistan

- DANA showed improvement in <TP> over time with no difference observed at Time 3 in concussed vs. controls.
- ANAM showed no improvement of concussed relative to non-concussed.
- Although the sample size was small, it seems that in this case DANA was more sensitive to changes over time for these concussed vs non-concussed patients.





Outline

Background

Feasibility and Reliability Data

Validity and Utility – Cross-Sectional Data

Longitudinal Validity – Sensitivity to Impairment over time

Clinical Studies

U.S. Army Rapid Innovation Fund

PTSD Study

- VA Pacific Island Healthcare System, Dr. Jim Spira (PHREI)
- 100 PTSD patients, receiving traditional (in clinic) vs. telehealth treatment
- Using DANA to track recovery over time

Concussion Study

- University of Wisconsin, (Dr. Alison Brooks)
- 66 student athletes (football), 33 concussed, 33 matched controls
- To assess cognitive function during recovery from moderate---severe TBI using the DANA

Depression Study

- **Johns Hopkins University Hospital, Dr. Adam Kaplin**
- **40 clinically depressed patients, ECT vs. non-ECT treatment**
- **Evaluation of the Cognitive and Behavioral Impact of ECT on the Treatment of Major Depressive Disorder**

Evaluation of the cognitive and behavioral impact of ECT on the treatment of major depressive disorder

Major Depressive Disorder (MDD)

A major source of morbidity and mortality in active military personnel and veterans often associated with cognitive impairment. Little is understood about the on-going cognitive effects of ECT on patients with MDD.

Study Objective

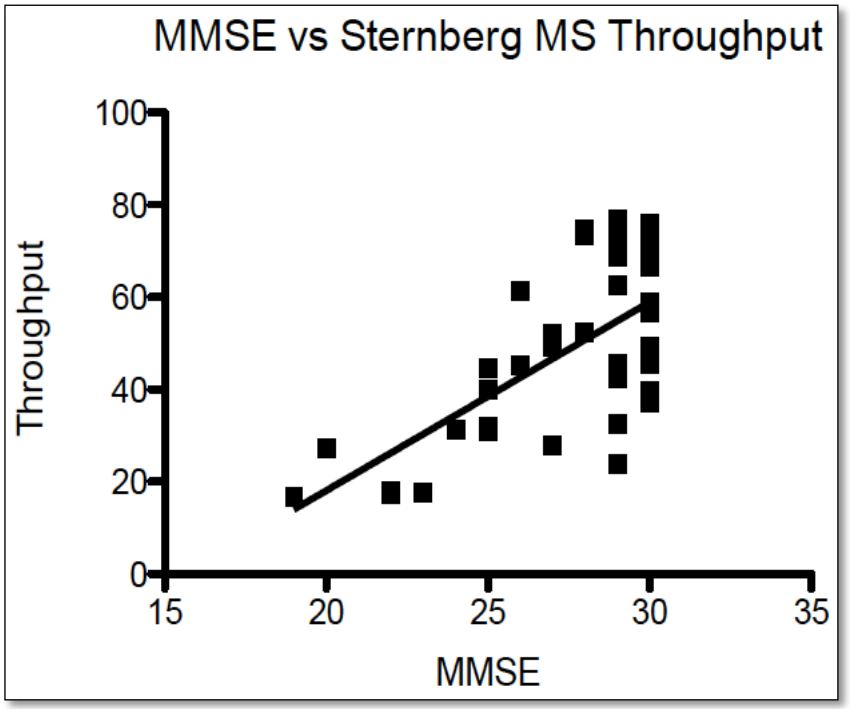
To measure cognitive changes in MDD patients during their course of ECT treatment (3 weeks)

Protocol

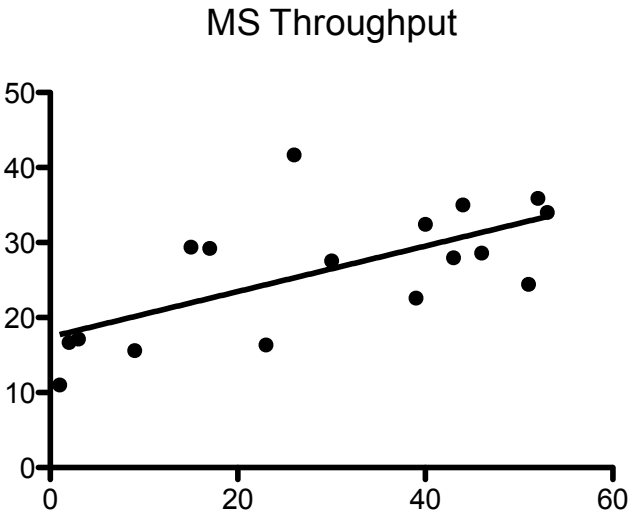
- Cognitive Assessments: twice a week
- Mini-Mental Status Exam (MMSE): 2-3 times per week
- *Subjects* n=20 ECT subjects, with n=20 control subjects undergoing other types of therapies
- Current Progress: 8 ECT, 14 Controls

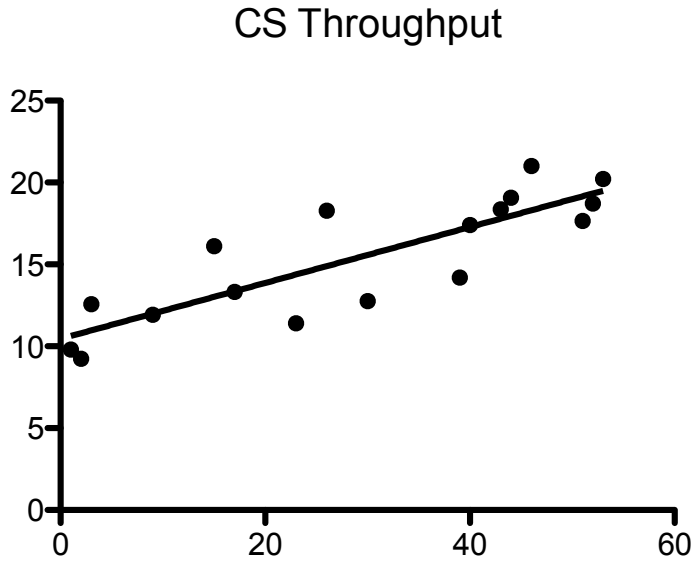
Results

- There is a high correlation between DANA and MMSE Results. (MHSRS Poster 2014)
- However MMSE shows a ceiling effect where as DANA throughput does not.

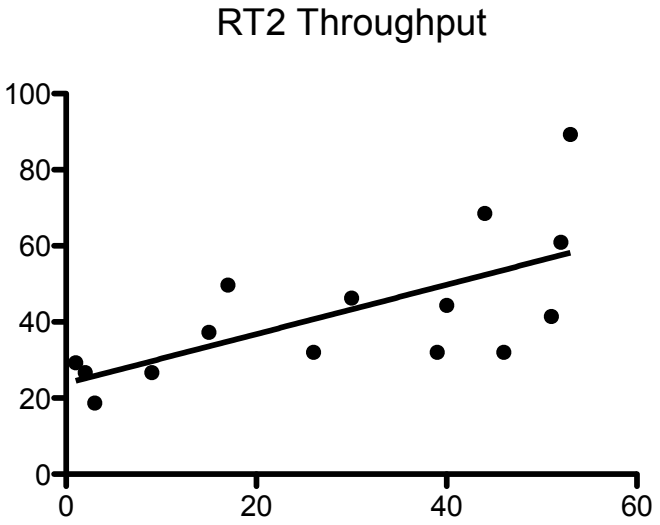


Sample Patient #1

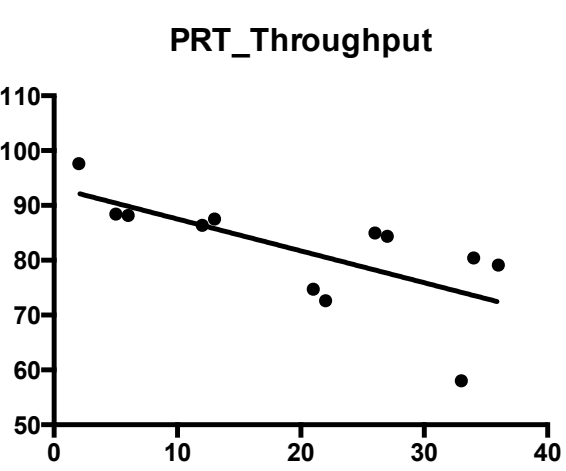


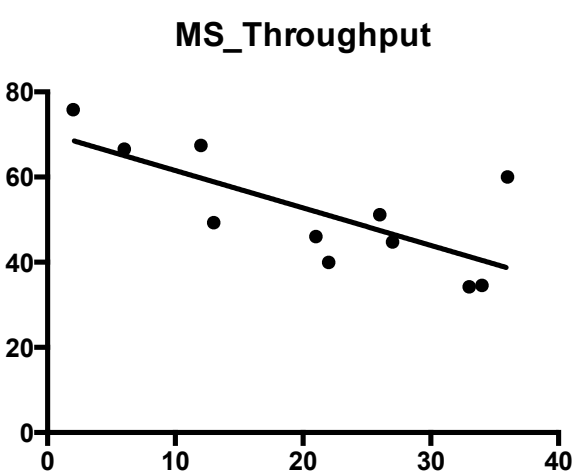


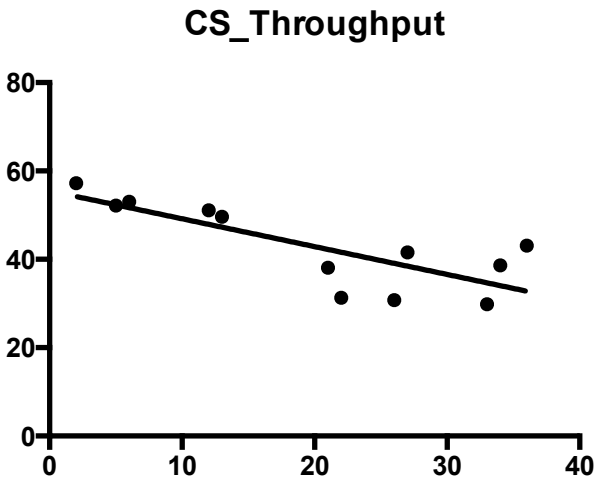
In this patient, MMSE = 30, but DANA shows cognitive improvement over the course of treatment.



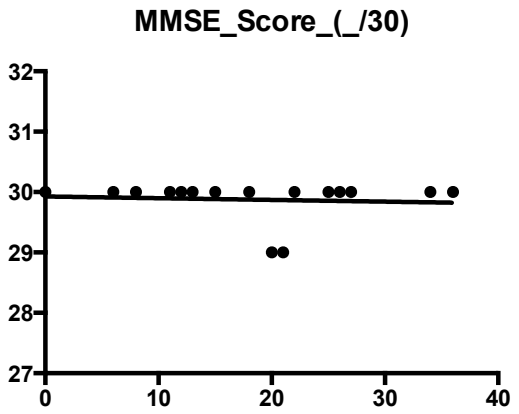
Sample Patient #2







In this patient, MMSE = 30, but DANA shows cognitive decline over the course of treatment.



DANA Partner Studies

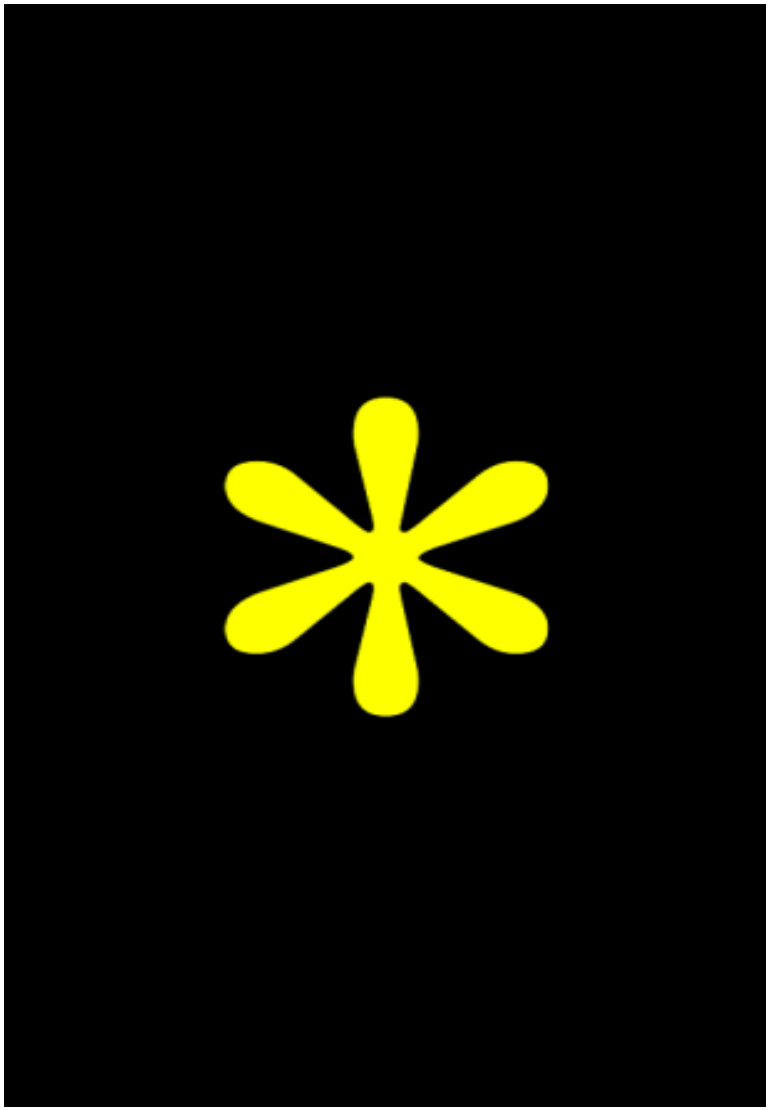
- US Coast Guard: POC: Michael Doria. Title: Neurocognitive assessment DoD/NCAA Sports Concussion study
- Navy Experimental Diving Unit: POC: Jay Haran. Title: Environmental testing to verify test-retest reliability among the same subjects in different environments.
- National Intrepid Center of Excellence (NICoE): POC: Douglas Brungart. Title: Assessing the Impact of Blast-Related Sensory Impairment on Multisensory Integration While Maneuvering on Foot
- Walter Reed Army Institute of Research (WRAIR): POC: Gary Kamimori. Title: Impact of caffeine on neurocognitive performance during sleep deprivation using the DANA.
- VA-New Jersey Health Care System (NJHCS) : POC: Rick Servatius. PTSD/TBI Study.

Thank You!

clathan@atinc.com

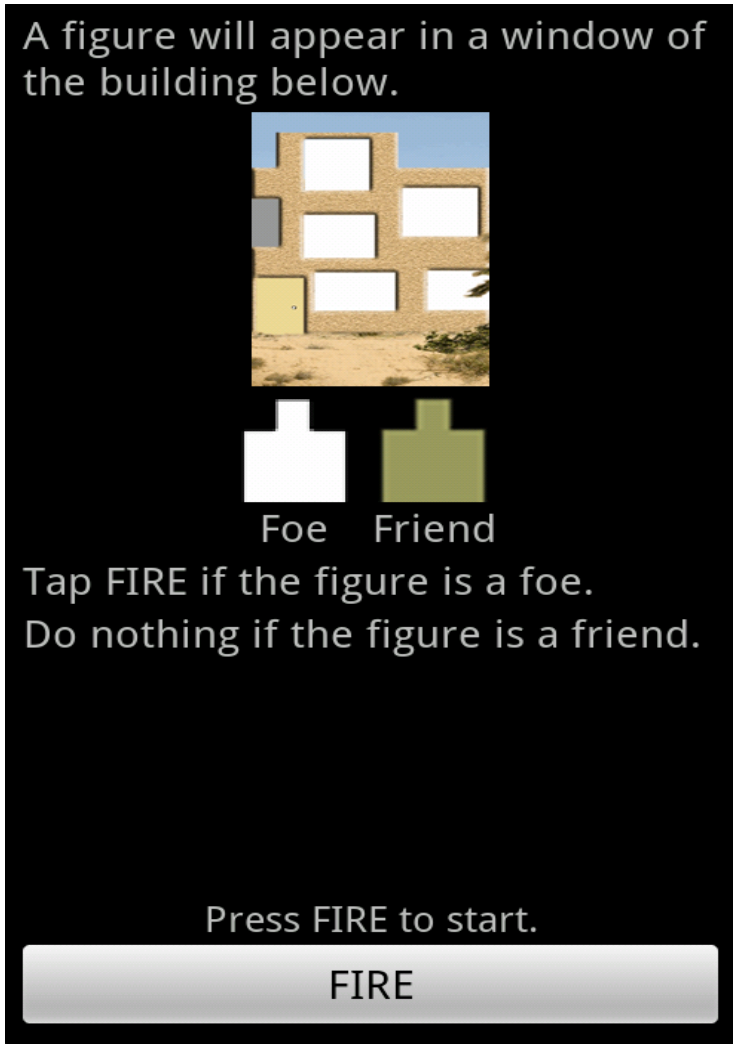
240-498-9471

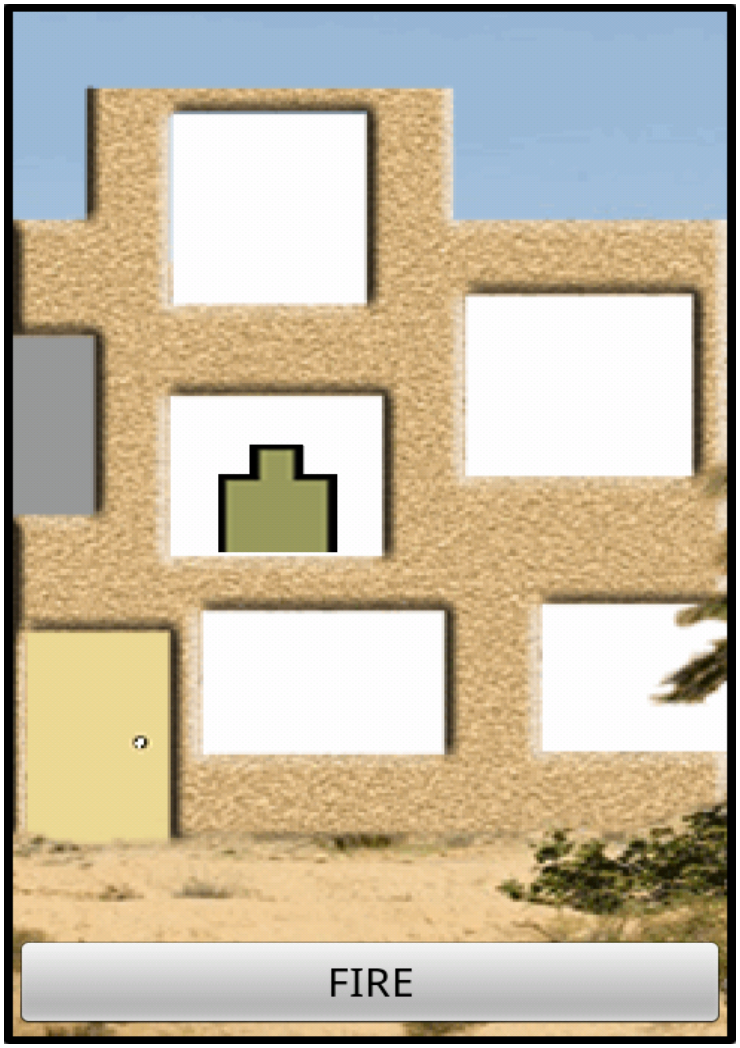
SIMPLE REACTION TIME (SRT)



PROCEDURAL REACTION TIME (PRO)

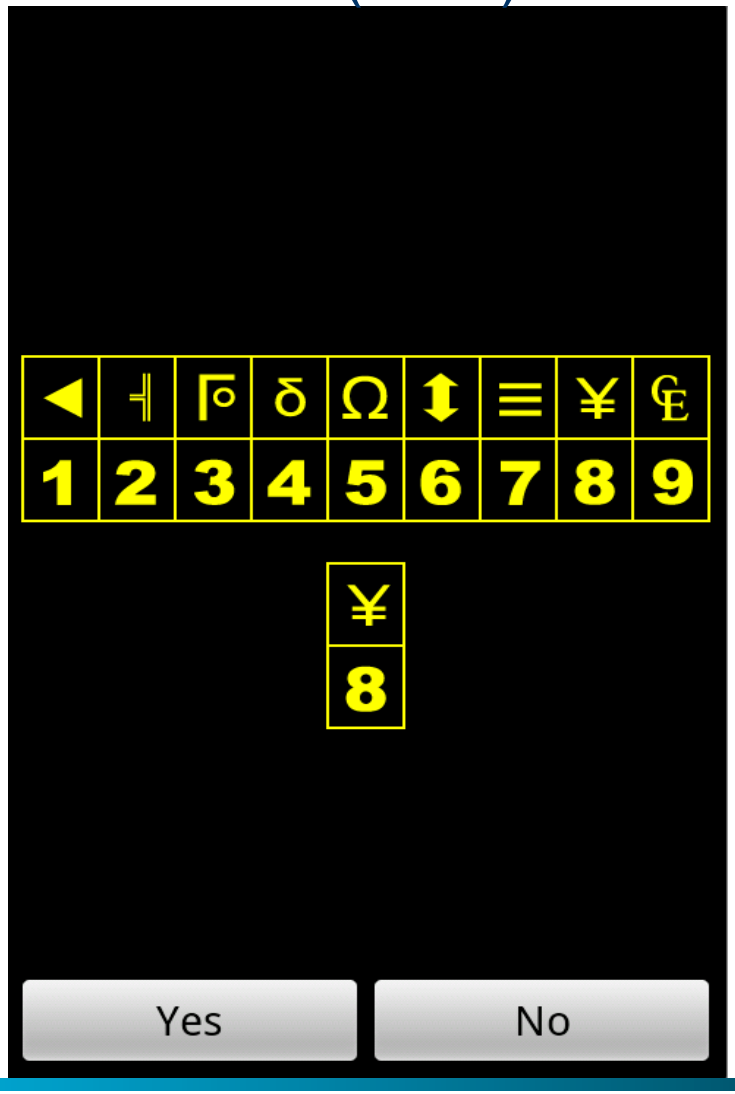
GO/NO-GO (GNG)


A figure will appear in a window of the building below.
Foe
Friend
Tap FIRE if the figure is a foe.
Do nothing if the figure is a friend.
Press FIRE to start.
FIRE

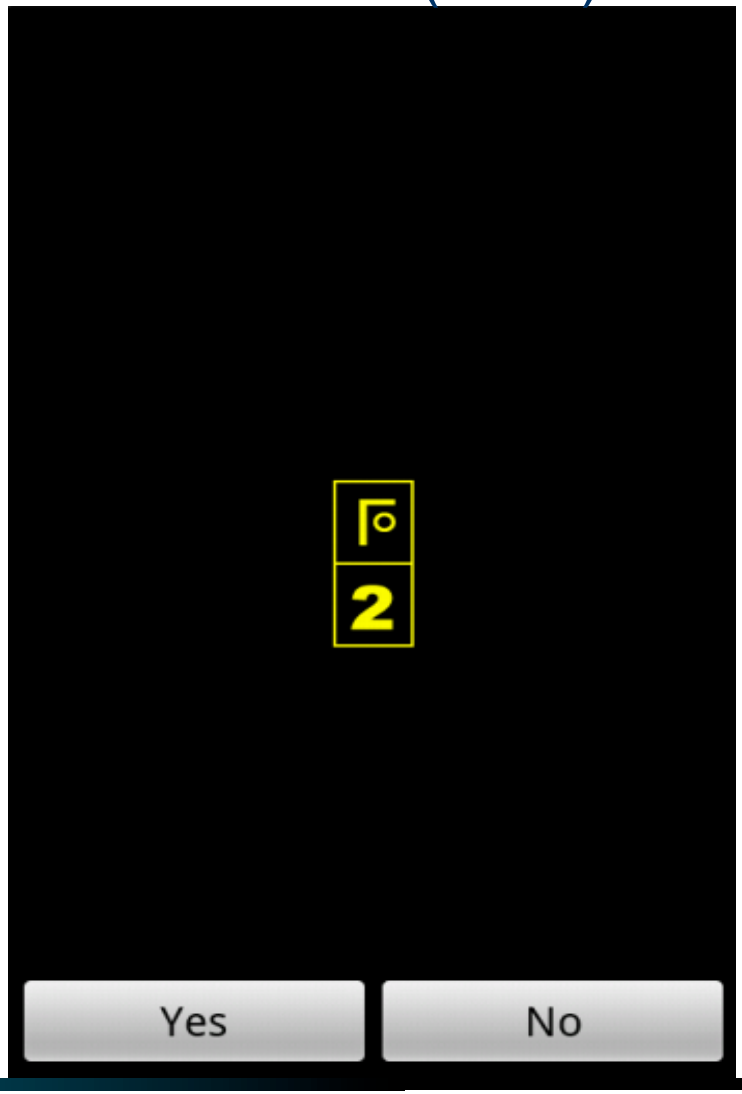

FIRE

CODE SUBSTITUTION

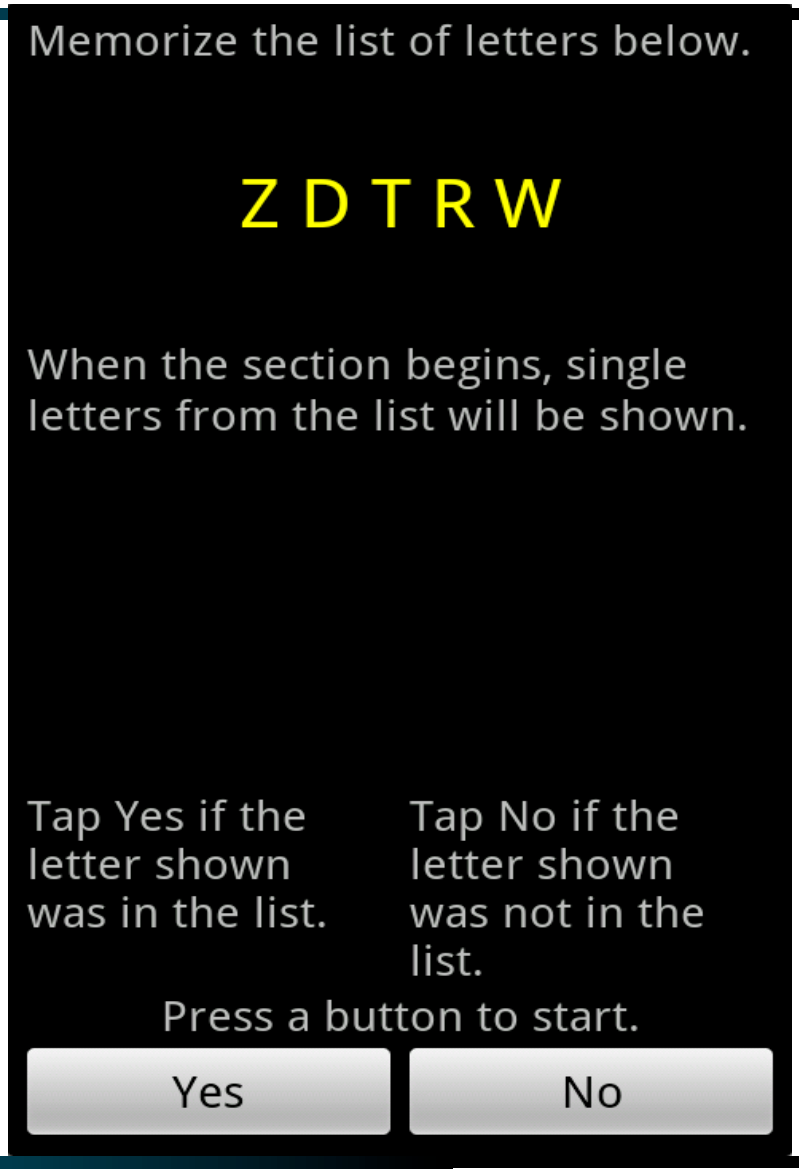
LEARNING (CDS)



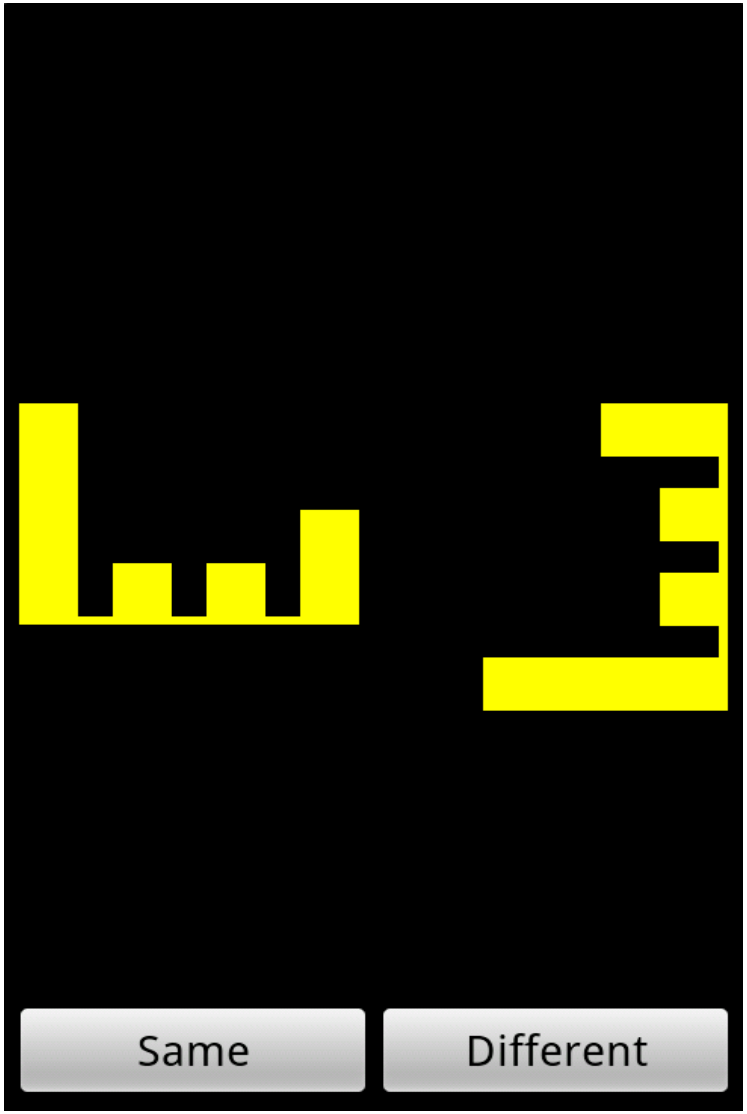
DELAYED (CDD)



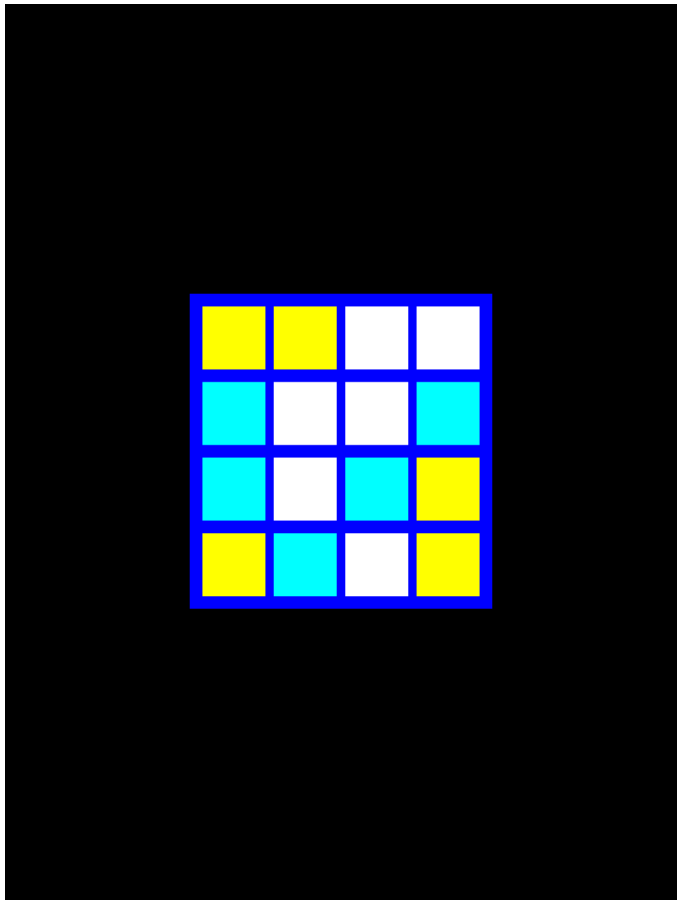
STERNBERG MEMORY SEARCH (STN)

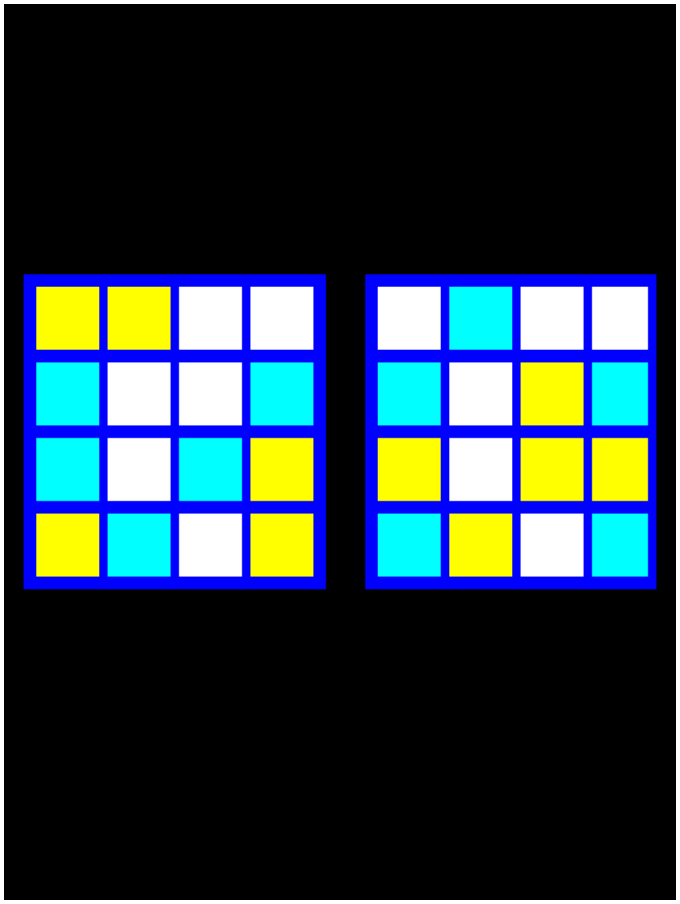


SPATIAL DISCRIMINATION (SPD)



Match to Sample (MSP)





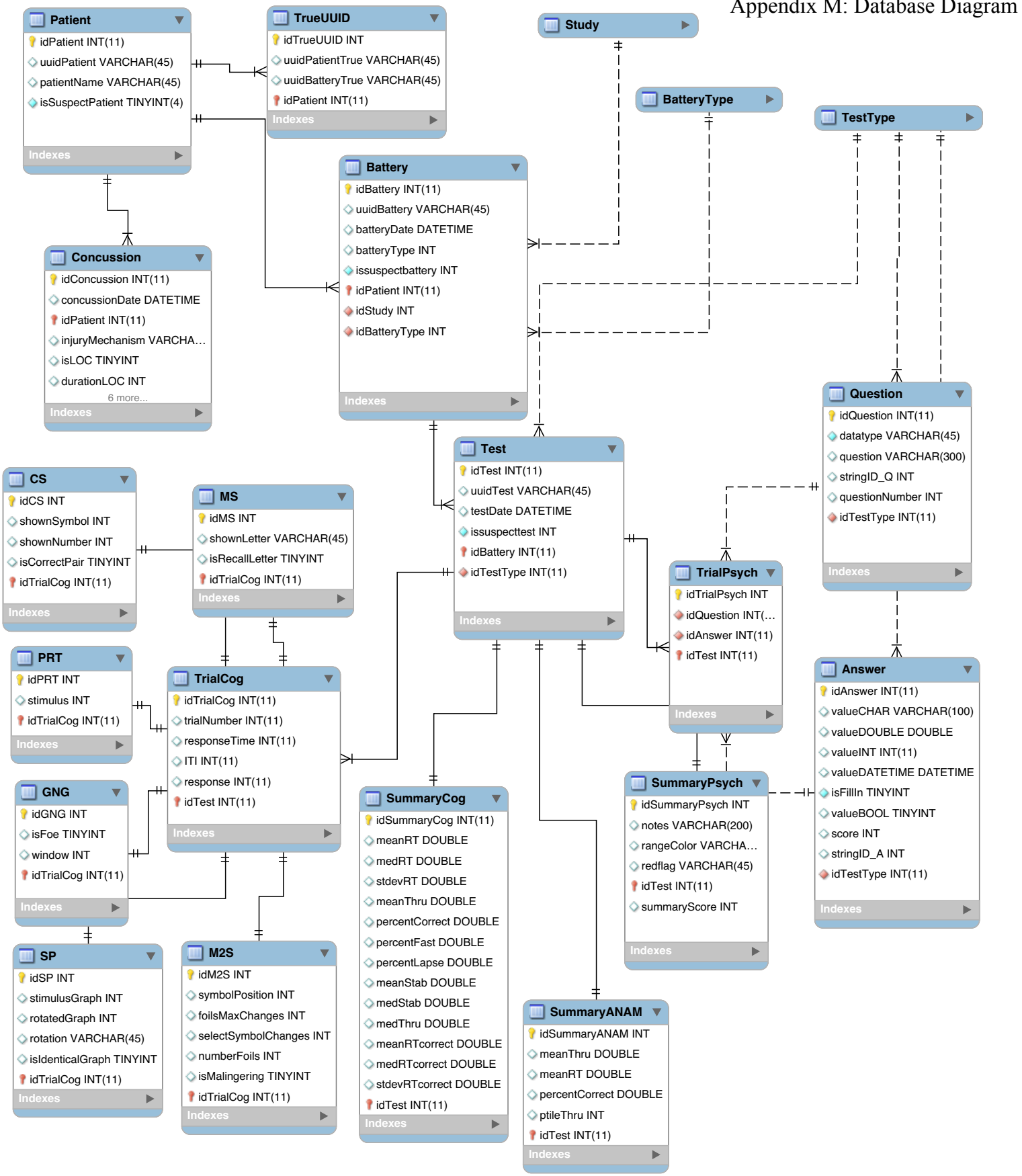
Psychological Screening Instrumen
- ISI (Insomnia Screening Index)
- PC-PTSD (4 item screener)

Psychological Clinical Measures:
- PCL-m (PTSD)
- PHQ-8/9 (depression)
- PSQI (insomnia).
- Deployment Stress Inventory (D
  (NBSI + anger/pain/distress)

Combat Exposure Scale (CES)

MACE

Appendix M: Database Diagram



University of Wisconsin – Brief Report (Controls versus Concussed)

Research Questions

1. Is there a difference in cognitive performance between controls and concussed University of Wisconsin athletes?

Participants

31 athletes from the University of Wisconsin completed DANA Standard. These 31 athletes are comprised of two groups. Nineteen of these athletes were part of the control who are made up of athletes who did not experience a concussion during the study period. The remaining 22 athletes made up the concussed group. These participants experienced a concussion during the study period. Each participant completed DANA Standard to obtain baseline measures in cognitive performance. Members of the control group completed DANA Standard, again, 8, 15, and 45 days after completing DANA Standard the first time (i.e. at baseline). Members of the concussed group completed DANA Standard within 24-hours of experiencing a concussion and then 8, 15, and 45 days post concussion.

Nineteen athletes in the control group completed DANA Standard at baseline. Of these 19 participants, 18 completed DANA Standard 8 days after baseline. Of the 19 participant who completed DANA Standard at baseline, 14 completed DANA Standard 15 days after baseline. Finally, of the original 19 participants, 10 completed DANA Standard 45 days after baseline. Of the concussed group, 22 athletes completed DANA Standard prior to experiencing a concussion. Of these 22 participants, 8 completed DANA Standard within 24 hours of experiencing a

concussion. Of the original 22 participants who completed DANA Standard at baseline, 16 completed DANA Standard 8 days post concussion. Of the original 22 participants, 14 completed DANA Standard 15 days post concussion. Finally, of the original 22 participants, 10 completed DANA Standard 45 days post concussion.

Methods

Anderson-Darling tests were performed to assess the normality of the data in order to determine which results, t-tests for normally distributed data and Wilcoxon ranksum for non-normally distributed data, to use to evaluate whether or not cognitive performance differed between the control group and the concussed group. T-tests and Wilcoxon ranksum were run to determine whether or not significant differences in cognitive performance exist between control participants and concussed participants. First, analyses were run comparing control participants' baseline cognitive performance to concussed participants' cognitive performance at each time interval (i.e. 24 hours, 8 days, 15 days, and 45 days post concussion). Secondly, analyses were run comparing non-concussed participants' and concussed participants' cognitive performance at the same time intervals (i.e. baseline, 8 days, 15 days, and 45 days).

Results

Control Baseline versus Concussed At Each Time Interval

Mean Reaction Time. The Anderson-Darling tests revealed that the *mean reaction times* for the control group baselines for all DANA subtests with the exception of the first administration of Simple Reaction Time (RT1) are normally distributed. Furthermore, these same tests revealed that *mean reaction times* for the concussed group are normally distributed with the exception of the following: RT1 at 24 hours and 15 days post concussion, Code

Substitution Delayed (CSD) 8 days post concussion, Procedural Reaction Time (PRT) 15 days post concussion, and Memory Search (MS) 15 and 45 days post concussion.

The t-tests and Wilcoxon ranksum results for *mean reaction times* are the same regardless of the normality of the data. With this in mind, the results in Table 1 indicate that there is no difference in *mean reaction time* for any DANA subtests between the control group baselines and the concussed group 24 hours post concussion (ps > .05). The results are similar for *mean reaction times* between the control group baselines and the concussed group 8 days post concussion (ps > .05). Table 2 shows no significant differences in *mean reaction time* between these two groups for any DANA subtest (ps > .05). The comparison between the control group baselines and the concussed group 15 days post concussion (Table 3) show that these two groups exhibited a near significant difference in *mean reaction times* on CSD (M_{Control} = 1044.58, SD_{Control} = 185.99, $M_{\text{Concussed}}$ = 1192.38, $SD_{\text{Concussed}}$ = 255.47) (t = -1.93; $p_{\text{t-test}}$ < .10). However, no other significant differences between *mean reaction times* for the aforementioned two groups exist based on the results shown in Table 3 (ps > .05). Finally, Table 4 demonstrates that no significant differences in *mean reaction times* exist between the control group baselines and the concussed group 45 days post concussion for any DANA subtest (ps > .05).

Mean Throughput. The Anderson-Darling tests show that *mean throughput* for the control group baselines for all DANA subtests with the exception of Match To Sample (MTS) are normally distributed. Additionally, these same tests show that *mean throughput* for the concussed group are normally distributed with the exception of the following: RT1 24 hours post concussion, MS 15 days post concussion, and MTS 45 days post concussion.

The t-tests and Wilcoxon ranksum results for *mean throughput* are similar regardless of normality. The results in Table 5 indicate that there is no difference in *mean throughput* for any

DANA subtests between the control group baselines and the concussed group 24 hours post concussion (*p*s > .05). The results are similar for mean throughput between the control group baselines and the concussed group 8 days post concussion. Table 6 shows no significant differences in *mean throughput* between these two groups for any DANA subtest (*p*s > .05). The comparison between the control group baselines and the concussed group 15 days post concussion (Table 7) show that these two groups differ significantly in *mean throughput* on CSD ($M_{Control}$ = 55.88, $SD_{Control}$ = 9.55, $M_{Concussed}$ = 48.37, $SD_{Concussed}$ = 9.56) (t = 9.53; $p_{t\text{-test}} < .05$)[1]. Thus, indicating that non-concussed participants have greater *mean throughput* on CSD than concussed participants who complete CSD 15 days following concussion. However, no other significant differences between *mean throughput* for the aforementioned two groups exist based on the results shown in Table 7 (*p*s > .05). Finally, Table 8 demonstrates that no significant differences in *mean throughput* exist between the control group baselines and the concussed group 45 days post concussion for any DANA subtest (*p*s > .05).

Percent Correct. Unlike *mean reaction times* and *mean throughput*, Anderson-Darling tests demonstrate that all of the *percent correct* data for the control group baselines is not normally distributed for all DANA subtests. Furthermore, Anderson-Darling tests demonstrate that the majority of the *percent correct* data for the concussed group is, also, not normally distributed for most of the DANA subtests with the exception of the following: Code Substitution Learning (CSL) 24 hours, 8 and 45 days post concussion, PRT 24 hours post concussion, MTS 24 hours, 8 and 45 days post concussion, MS 24 hours and 15 days post concussion, and Spatial Processing (SP) 15 days post concussion.

[1] T-test results rather than Wilcoxon ranksum are provided because data from both groups is normally distributed as reported in the previous paragraph.

The findings for *percent correct* are similar to those for *mean throughput*, for the most part (see Tables 9 through 12), regardless of data normality. Table 9 indicates that there is a near significant difference in GNG *percent correct* between the control group baselines ($M = 97.72$, $SD = 2.73$) and the concussed group 24 hours post concussion ($M = 99.58$, $SD = 1.18$) ($p_{Wilcoxon} < .10$)[2]. The results also reveal a significant difference in CSD *percent correct* between the control group baselines ($M = 92.84$, $SD = 6.16$) and the concussed group 24 hours post concussion ($M = 89.24$, $SD = 3.13$) ($p_{Wilcoxon} < .05$). Consequently, this finding suggests that 24 hours post concussion participants respond correctly to fewer questions on CSD than non-concussed participants. Table 9 reveals that there are no other significant differences in *percent correct* between the control group baselines and the concussed group 24 hours post concussion on the remaining DANA subtests ($ps > .10$).

The second administration of Simple Reaction Time (RT2) *percent correct* is significantly different between the control group baselines ($M = 97.24$, $SD = 2.99$) and the concussed group 8 days post concussion ($M = 99.22$, $SD = 1.51$) ($p_{Wilcoxon} < .05$), as shown in Table 10. Surprisingly, this result indicates that the concussed group responds correctly more often on RT2 than non-concussed participants. Again, no significant differences in *percent correct* between the control group baselines and the concussed group 8 days post concussion is illustrated in Table 10 ($ps > .10$).

The results regarding *percent correct* between the control group baselines and the concussed group 15 days post concussion are shown in Table 11. The outcomes shown in this table demonstrate that RT1 *percent correct* differs significantly between the control group baselines ($M = 99.61$, $SD = 1.25$) and the concussed group 15 days post concussion ($M = 96.79$,

[2] Wilcoxon ranksum results are provided because data from both groups is not normally distributed as reported in the previous paragraph.

SD = 5.41) ($p_{Wilcoxon} < .05$). This outcome implies that 15 days following concussion, concussed participants respond more incorrectly on RT1 than non-concussed participants. Table 11 also reveals a nearly significant difference on PRT *percent correct* between the control group baselines (*M* = 95.56, *SD* = 3.35) and the concussed group 15 days following concussion (*M* = 97.55, *SD* = 2.79) ($p_{Wilcoxon} < .10$). No significant differences are demonstrated on *percent correct* between the control group baselines and the concussed group 15 days post concussion on any of the remaining DANA subtests (*p*s > .10).

Finally, Table 12 shows a significant difference in CSL *percent correct*, PRT *percent correct*, and GNG *percent correct* between the control group baselines (*M* = 94.44, *SD* = 3.76; *M* = 95.56, *SD* = 3.35; *M* = 97.72, *SD* = 2.73; respectively) and the concussed group 45 days post concussion (*M* = 98.06, *SD* = 1.63; *M* = 98.13, *SD* = 2.19; *M* = 99.67, *SD* = 1.05; respectively) ($ps_{Wilcoxon} < .05$). Each of these results suggest that 45 days following concussion, concussed participants respond more correctly on CSL, PRT, and GNG than non-concussed participants. None of the *percent correct* scores on the remaining DANA subtests are significantly different between the control group baselines and the concussed group 45 days post concussion.

Control versus Concussed At The Same Time Intervals

Mean Reaction Time. The Anderson-Darling tests revealed that the *mean reaction times* for the control group are normally distributed for all DANA subtests with the exception of the following: RT1 at baseline and 8 and 15 days post baseline, and PRT 8 and 15 days post baseline, and SP 8 days post baseline. Furthermore, the Anderson-Darling tests revealed that *mean reaction times* for the concussed group are normally distributed with the exception of the following: GNG at baseline, CSD 8 days post concussion, RT1 15 days post concussion, PRT 15 days post concussion, and MS 15 and 45 days post concussion.

The results in Table 13 indicate that there is a significant difference in baseline CSD *mean reaction time* between the control group (M = 1044.58, SD = 185.99) and the concussed group (M = 1189.62, SD = 225.44) (t = -2.23, $p < .05$) at baseline. This outcome suggests that CSD *mean reaction time* is slower, on average, for the concussed group before experiencing a concussion than for the control group. Table 13 shows that there are no significant differences in baseline *mean reaction times* between the control group and the concussed group on any of the remaining DANA subtests (ps > .05). There is no difference in *mean reaction times* between the control group 8 days post baseline and the concussed group 8 days post concussion for any DANA subtests (ps > .05), as shown in Table 14.

On the other hand, Table 15 illustrates that there is a near significant difference in CSL and SP *mean reaction time* between the control group 15 days post baseline (M = 1099.02, SD = 144.13; M = 1226.49, SD = 208.42; respectively) and the concussed group 15 days post concussion (M = 1366.80, SD = 248.20; M = 1540.89, SD = 276.29; respectively) (t = -1.88, $p < .10$; t = -1.75, $p < .10$; respectively). Conversely, Table 15 also shows that there is no significant difference in *mean reaction times* 15 days post baseline for the control group and 15 days post concussion for the concussed group on any of the remaining DANA subtests (ps > .05). Finally, *mean reaction times* between the control group 45 days post baseline and the concussed group 45 days post concussion are not significantly different (ps > .05), as shown in Table 16.

Mean Throughput. The Anderson-Darling tests show that *mean throughput* for the control group for all DANA subtests are normally distributed with the exception of the following: MTS at baseline, RT1 8 days post baseline, and PRT 8 days post baseline. Additionally, the Anderson-Darling tests show that *mean throughput* for the concussed group are

normally distributed with the exception of the following: GNG at baseline, CSD at baseline, MS 15 days post concussion, and MTS 45 days post concussion. The only significant difference in *mean throughput* between the control group and the concussed group occurs at baseline on CSD ($M = 55.88$, $SD = 9.55$; $M = 46.94$, $SD = 9.13$; respectively) ($p_{\text{Wilcoxon}} < .05$), shown in Table 17. This finding implies that CSD *mean throughput* is greater for the control group than for the concussed group prior to experiencing a concussion. Table 17 also shows that there are no significant differences in *mean throughput* for any remaining DANA subtest at baseline ($ps > .05$). Moreover, there are no significant differences in *mean throughput* on any DANA subtests between the control group at 8, 15, and 45 days post baseline and the concussed group 8, 15, and 45 days post concussion ($ps > .05$), respectively, as shown in Tables 18 through 20.

Percent Correct. Unlike *mean reaction times* and *mean throughput*, Anderson-Darling tests demonstrate that all of the *percent correct* data for the control group is not normally distributed for all DANA subtests with the exception of the following: CSL 8 and 45 days post baseline, SP 8 and 15 days post baseline, CSD 15 days post baseline, and MTS 45 days post baseline. Furthermore, Anderson-Darling tests demonstrate that the majority of the *percent correct* data for the concussed group is, also, not normally distributed for the DANA subtests with the exception of the following: CSD at baseline and 15 days post concussion, CSL 8 and 45 days post concussion, MTS 8, 15, and 45 days post concussion, and SP 15 days post concussion.

The results of *percent correct* between control and concussed groups at equivalent time intervals are provided in Tables 21 through 24. Beginning with baseline *percent correct*, Table 21 shows that baseline RT2, CSD, and MS *percent correct* scores are significantly different between the control group ($M = 97.24$, $SD = 2.99$; $M = 92.84$, $SD = 6.16$; $M = 82.63$, $SD = 19.89$; respectively) and the concussed group ($M = 98.64$, $SD = 3.06$; $M = 88.76$, $SD = 7.30$; $M = 71.21$,

SD = 23.27; respectively) (p_{Wilcoxon}s < .05). These results suggests that *percent correct* on RT2 is higher for the concussed group before sustaining a concussion than the control group at baseline. Regarding CSD and MS, the aforementioned significant results imply that *percent correct* on CSD and MS is lower for the concussed group before sustaining a concussion than for the control group at baseline. Additionally, Table 21 shows that CSL *percent correct* scores are nearly significantly different between the control group and the concussed group at baseline (p_{Wilcoxon} < .10). Lastly, Table 21 indicates that there are no significant differences in *percent correct* between the control group and the concussed group at baseline on any of the remaining DANA subtests (p_{Wilcoxon}s > .05).

Percent correct scores 8 days post baseline for the control group and 8 days post concussion for the concussed group are not significantly different (p_{Wilcoxon}s > .05), as shown in Table 22. The results are similar for *percent correct* scores 15 days post baseline and 15 days post concussion, as shown in Table 23 ($p_{\text{t-test}}$s > .05 for SP and CSD; p_{Wilcoxon}s > .05 for remaining DANA subtests)[3]. Table 24 presents the results of *percent correct* 45 days post baseline for the control group and 45 days post concussion for the concussed group. As shown, these two groups differ significantly on *percent correct* scores on RT1 (*M* = 98.65, *SD* = 2.19; *M* = 100.00, *SD* = 0.00; respectively) (p_{Wilcoxon} < .05). This outcome suggests that *percent correct* is higher for concussed participants 45 days post concussion than for non-concussed participants 45 days post baseline. Along with these findings, Table 24 demonstrates that *percent correct* scores are nearly significantly different between the control group 45 days post baseline and the concussed group 45 days post concussion on CSL (*M* = 95.51, *SD* = 4.21; *M* = 98.06, *SD* = 1.63; respectively) and SP (*M* = 89.62, *SD* = 7.21; *M* = 94.50, *SD* = 4.38;

[3] *Percent correct* for SP and CSD for both groups is normally distributed, as reported earlier, thus t-test results are reported.

respectively) ($p_{\text{t-test}}s < .10$). Finally, Table 24 shows no significant differences in *percent correct* scores between the control group 45 days post baseline and the concussed group 45 days post concussion on any of the remaining DANA subtests ($ps > .05$).

Conclusion

Research Question 1. There is a significant difference in cognitive performance between the control group baselines and the concussed group at various time intervals on certain aspects of DANA subtests. Control group baselines on CSD *mean throughput* is higher, on average, than CSD *mean throughput* for the concussed group 15 days post concussion. *Percent correct* at baseline for the control group, on average, is higher than the concussed group CSD *percent correct* 24 hours post concussion. Interestingly, RT2 *percent correct* at baseline for the control group is *lower*, on average than *percent correct* for the concussed group 8 days post concussion.

Much like with the control group baselines versus the concussed group at different time intervals, control group cognitive performance at equivalent time points as that of the concussed group are significantly different for certain aspects of DANA subtests. *Mean reaction time* at baseline for the control group is faster, on average, than for the concussed group at baseline. Furthermore, *mean throughput* at baseline for the control group is higher, on average, than for the concussed group at baseline. Finally, RT2 *percent correct* is lower, on average, for the control group at baseline than for the control group at baseline. On the other hand, CSD and MS *percent correct* at baseline is higher, on average, for the control group at baseline than for the control group at baseline. Additionally, RT1 *percent correct* 45 days post baseline for the control group is lower, on average, than for the concussed group 45 days post concussion.

Figures and Tables

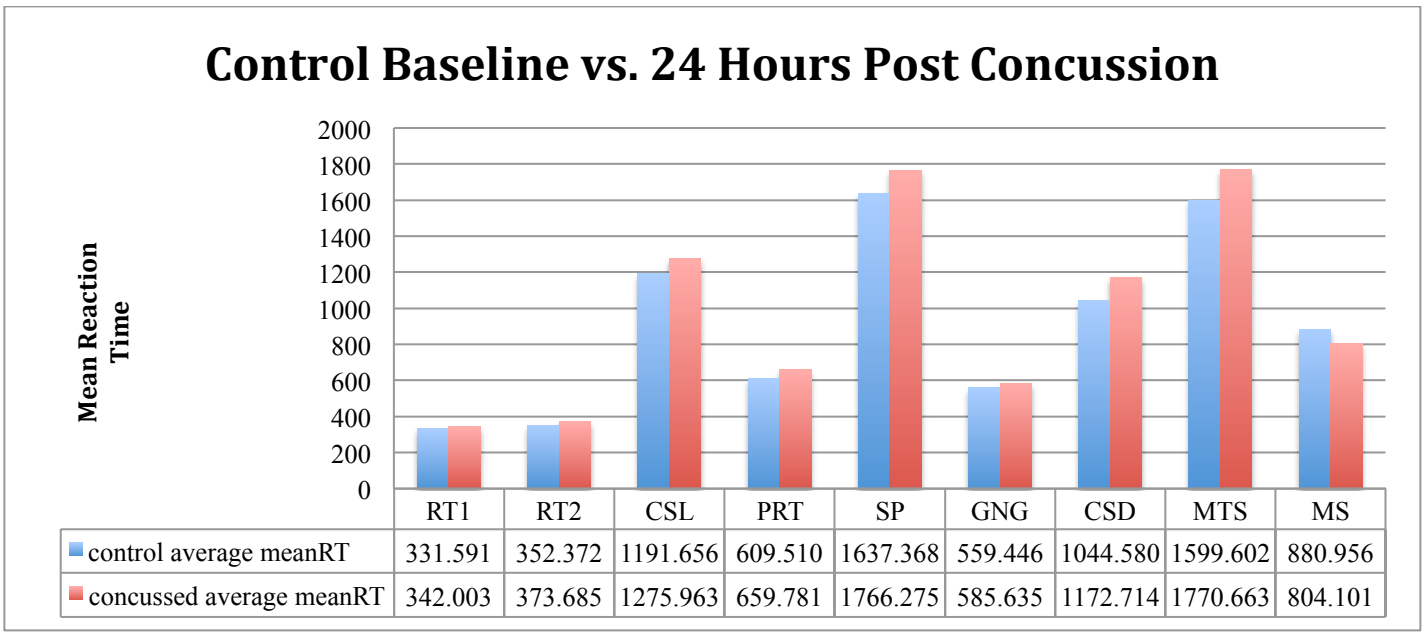


Table 1. Control Baselines vs. Concussed (24-hour Post Concussion): Mean Reaction Time.

	Control		Concussed		T-test Results			Wilcoxon
	meanRT (*M*)	meanRT (*SD*)	meanRT (*M*)	meanRT (*SD*)	*t* (*SD*)	*t*	*p*	*p*
RT1	331.591	60.778	342.003	69.620	63.378	-0.390	0.700	0.577
RT2	352.372	64.683	373.685	58.672	63.058	-0.802	0.430	0.541
CSL	1191.656	209.185	1275.963	91.619	184.001	-1.087	0.287	0.105
PRT	609.510	96.054	659.781	66.888	88.858	-1.342	0.192	0.130
SP	1637.368	349.335	1766.275	301.114	336.530	-0.909	0.372	0.353
GNG	559.446	88.338	585.635	80.464	86.206	-0.721	0.478	0.473
CSD	1044.580	185.994	1172.714	256.469	208.147	-1.461	0.157	0.159
MTS	1599.602	368.970	1770.663	165.192	325.055	-1.249	0.223	0.212
MS	880.956	158.446	804.101	142.501	154.148	1.183	0.248	0.614

$N_{Control}$ = 19; $N_{Concussed}$ = 8.

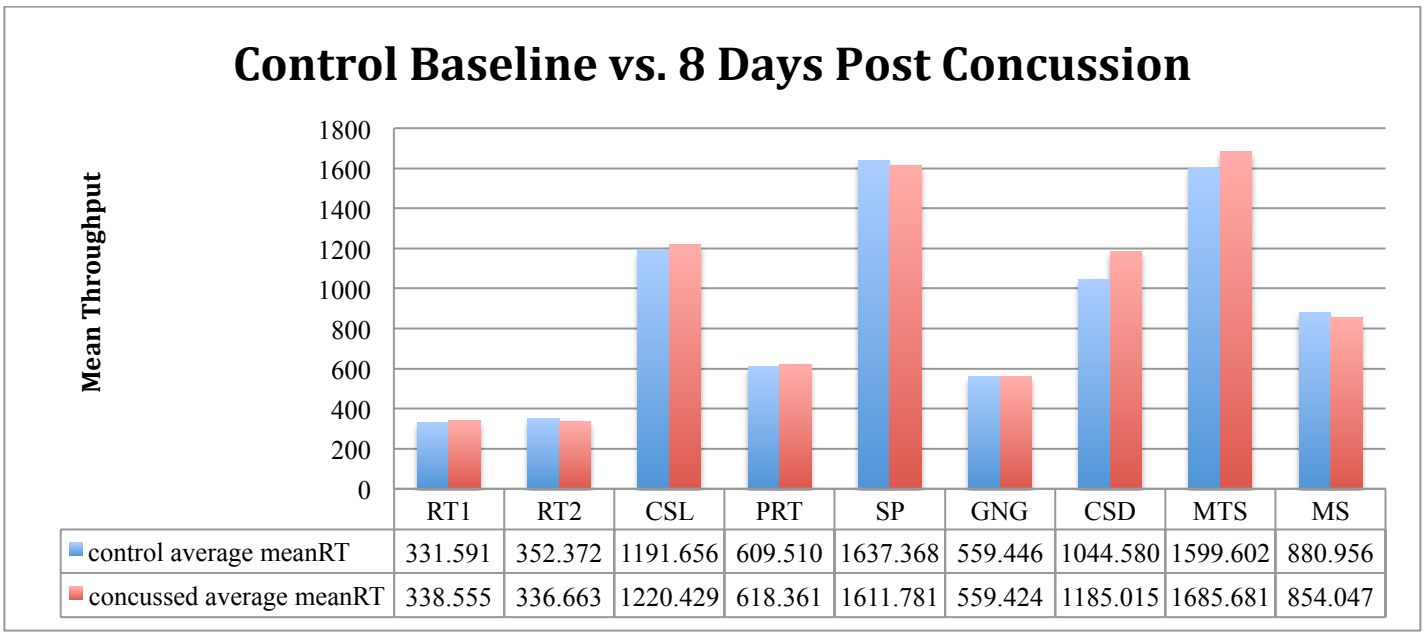


Table 2. Control Baselines vs. Concussed (8 Days Post Concussion): Mean Reaction Time.

	Control		Concussed		T-test Results			Wilcoxon
	meanRT (*M*)	meanRT (*SD*)	meanRT (*M*)	meanRT (*SD*)	*t* (*SD*)	*t*	*p*	*p*
RT1	331.591	60.778	338.555	52.533	57.178	-0.359	0.722	0.540
RT2	352.372	64.683	336.663	44.591	56.444	0.820	0.418	0.417
CSL	1191.656	209.185	1220.429	223.772	215.938	-0.393	0.697	0.855
PRT	609.510	96.054	618.361	90.298	93.482	-0.279	0.782	0.703
SP	1637.368	349.335	1611.781	354.023	351.474	0.215	0.831	0.655
GNG	559.446	88.338	559.424	90.291	89.231	0.001	0.999	0.830
CSD	1044.580	185.994	1185.015	344.811	270.023	-1.533	0.135	0.362
MTS	1599.602	368.970	1685.681	329.130	351.421	-0.722	0.475	0.631
MS	880.956	158.446	854.047	259.578	210.526	0.377	0.709	0.562

$N_{Control}$ = 19; $N_{Concussed}$ = 16.

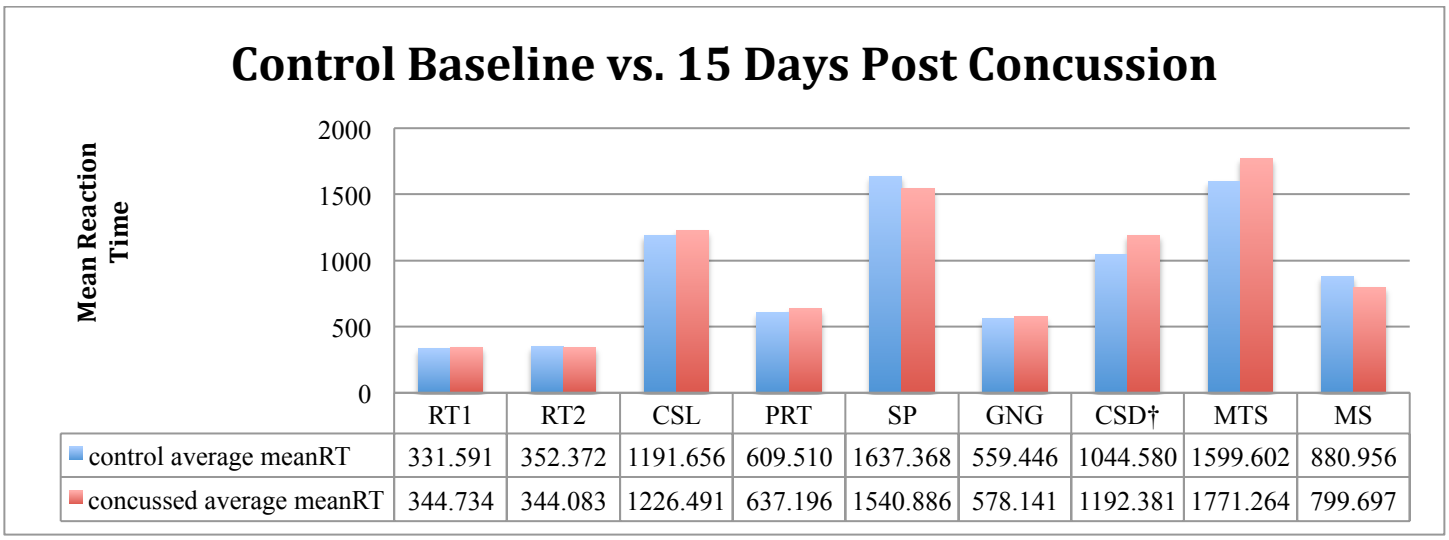


Table 3. Control Baselines vs. Concussed (15 Days Post Concussion): Mean Reaction Time.

	Control		Concussed		T-test Results			Wilcoxon
	meanRT (*M*)	meanRT (*SD*)	meanRT (*M*)	meanRT (*SD*)	*t* (*SD*)	*t*	*p*	*p*
RT1	331.591	60.778	344.734	71.621	65.544	-0.569	0.573	0.623
RT2	352.372	64.683	344.083	47.847	58.218	0.404	0.689	0.785
CSL	1191.656	209.185	1226.491	208.422	208.865	-0.474	0.639	0.372
PRT	609.510	96.054	637.196	154.840	124.143	-0.633	0.531	0.870
SP	1637.368	349.335	1540.886	276.292	320.736	0.854	0.400	0.334
GNG	559.446	88.338	578.141	111.317	98.628	-0.538	0.594	0.785
CSD	1044.580	185.994	1192.381	255.468	217.843	-1.926	0.063	0.071
MTS	1599.602	368.970	1771.264	408.165	385.892	-1.263	0.216	0.353
MS	880.956	158.446	799.697	218.689	186.099	1.240	0.224	0.572

$N_{Control} = 19$; $N_{Concussed} = 14$.

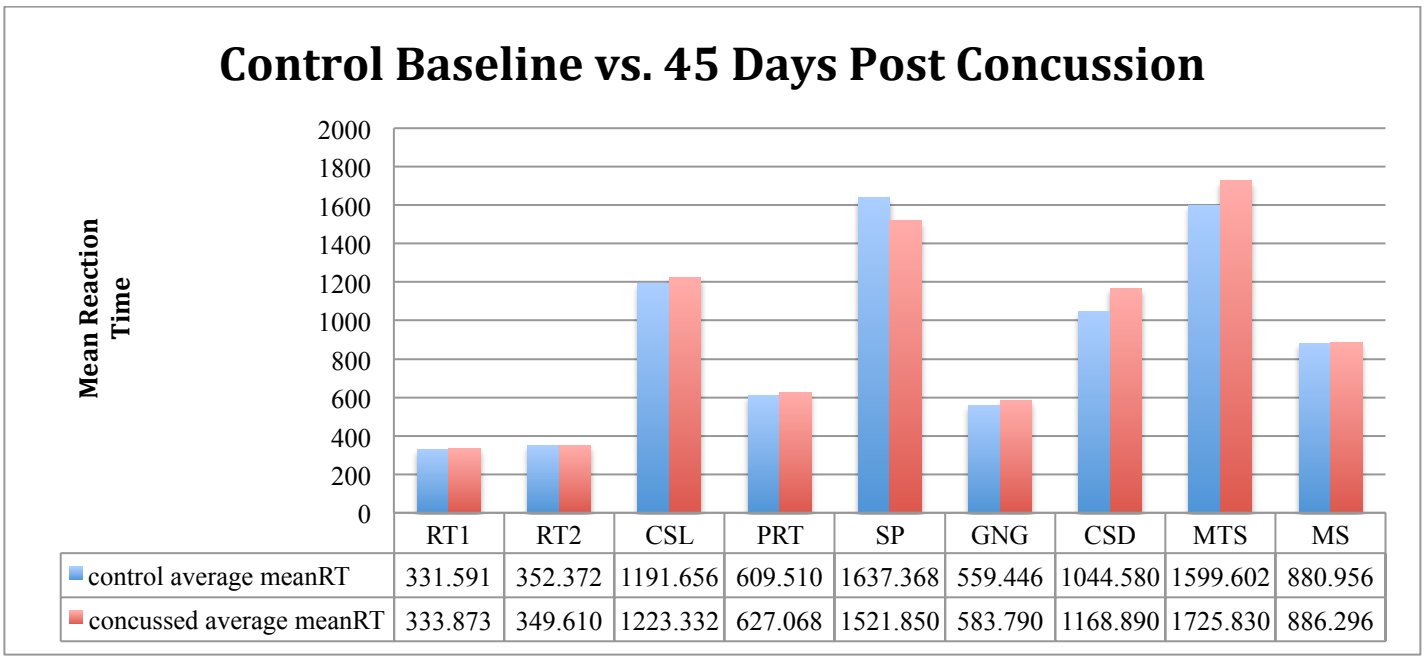


Table 4. Control Baselines vs. Concussed (45 Days Post Concussion): Mean Reaction Time.

	Control		Concussed		T-test Results			Wilcoxon
	meanRT (*M*)	meanRT (*SD*)	meanRT (*M*)	meanRT (*SD*)	*t* (*SD*)	*t*	*p*	*p*
RT1	331.591	60.778	333.873	36.570	53.930	-0.108	0.915	0.551
RT2	352.372	64.683	349.610	38.211	57.236	0.124	0.903	1.000
CSL	1191.656	209.185	1223.332	169.054	196.720	-0.412	0.683	0.536
PRT	609.510	96.054	627.068	106.451	99.640	-0.451	0.656	0.766
SP	1637.368	349.335	1521.850	239.655	317.020	0.933	0.359	0.281
GNG	559.446	88.338	583.790	95.360	90.739	-0.687	0.498	0.663
CSD	1044.580	185.994	1168.890	293.503	227.546	-1.398	0.173	0.281
MTS	1599.602	368.970	1725.830	269.019	338.944	-0.953	0.349	0.371
MS	880.956	158.446	886.296	153.209	156.720	-0.087	0.931	0.396

$N_{Control}$ = 19; $N_{Concussed}$ = 10.

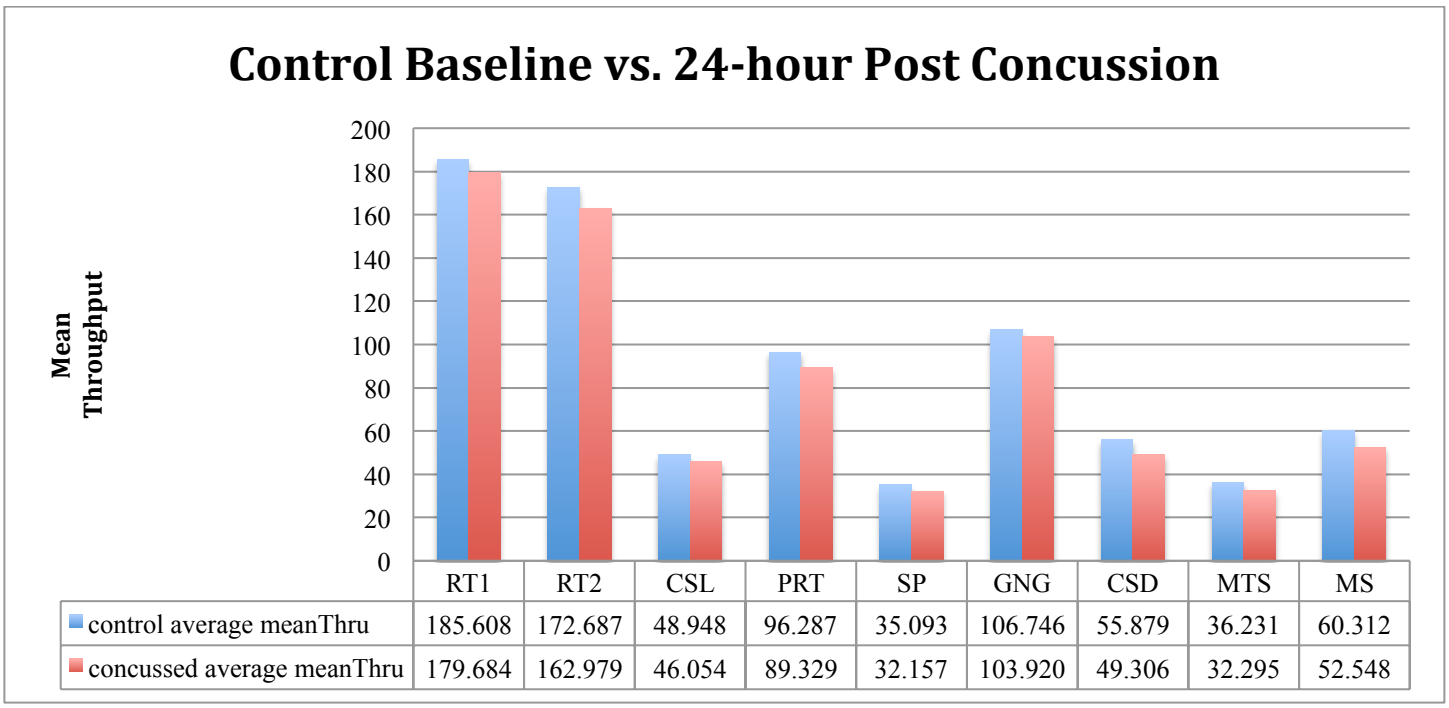


Table 5. Control Baselines vs. Concussed (24-hours Post Concussion): Mean Throughput.

	Control		Concussed		T-test Results			Wilcoxon
	meanThru (*M*)	meanThru (*SD*)	meanThru (*M*)	meanThru (*SD*)	*t* (*SD*)	*t*	*p*	*p*
RT1	185.608	29.594	179.684	27.776	29.096	0.483	0.633	0.577
RT2	172.687	30.439	162.979	26.526	29.396	0.784	0.441	0.690
CSL	48.948	7.085	46.054	2.826	6.195	1.108	0.278	0.212
PRT	96.287	13.929	89.329	8.712	12.686	1.301	0.205	0.212
SP	35.093	7.200	32.157	6.454	6.999	0.996	0.329	0.326
GNG	106.746	15.947	103.920	15.809	15.908	0.421	0.677	0.730
CSD	55.879	9.550	49.306	8.277	9.211	1.693	0.103	0.105
MTS	36.231	11.311	32.295	3.664	9.792	0.954	0.349	0.730
MS	60.312	17.224	52.548	24.415	19.507	0.944	0.354	0.507

$N_{Control}$ = 19; $N_{Concussed}$ = 8.

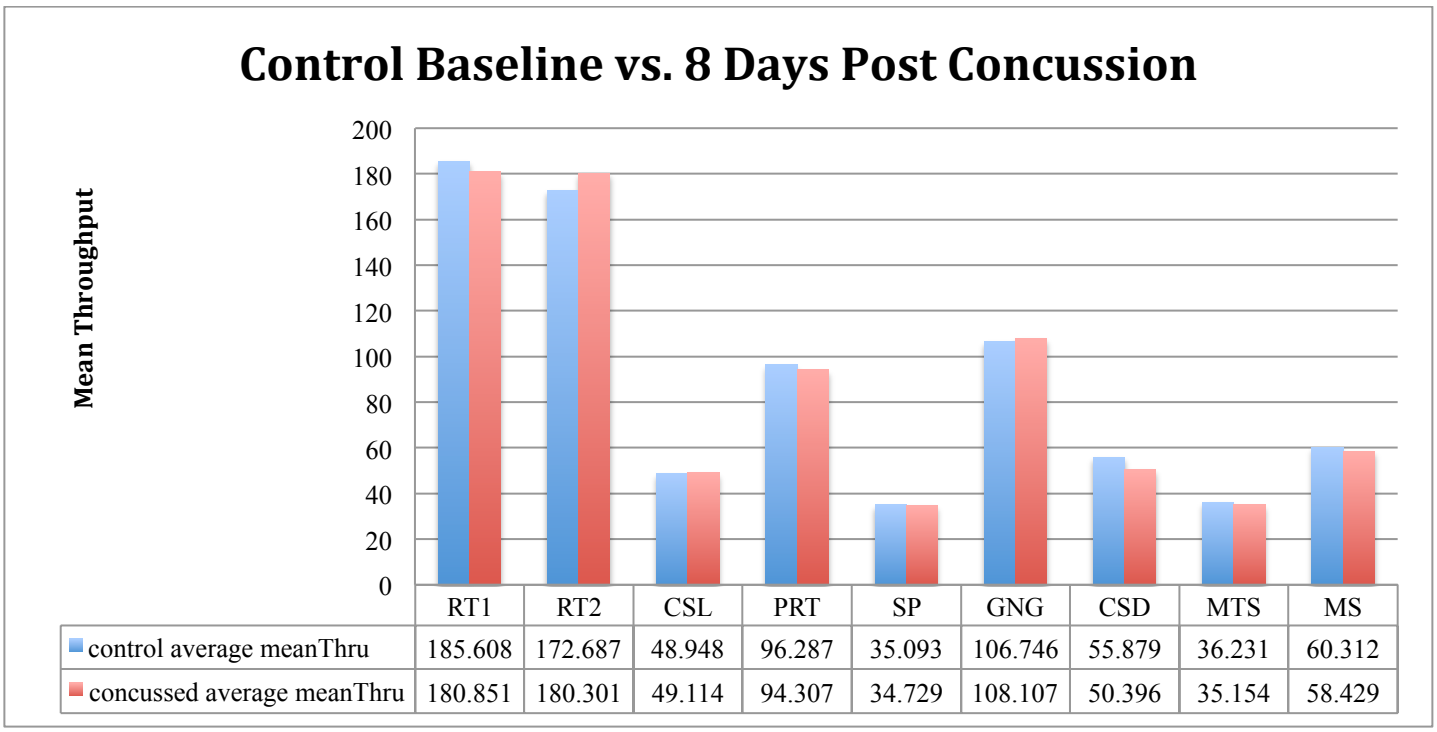


Table 6. Control Baselines vs. Concussed (8 Days Post Concussion): Mean Throughput.

	Control		Concussed		T-test Results			Wilcoxon
	meanThru (*M*)	meanThru (*SD*)	meanThru (*M*)	meanThru (*SD*)	*t* (*SD*)	*t*	*p*	*p*
RT1	185.608	29.594	180.851	26.936	28.416	0.493	0.625	0.540
RT2	172.687	30.439	180.301	22.940	27.287	-0.822	0.417	0.345
CSL	48.948	7.085	49.114	9.357	8.196	-0.060	0.953	0.855
PRT	96.287	13.929	94.307	12.687	13.379	0.436	0.666	0.728
SP	35.093	7.200	34.729	5.938	6.656	0.161	0.873	0.804
GNG	106.746	15.947	108.107	17.424	16.635	-0.241	0.811	0.987
CSD	55.879	9.550	50.396	13.652	11.596	1.394	0.173	0.329
MTS	36.231	11.311	35.154	7.657	9.820	0.323	0.748	0.804
MS	60.312	17.224	58.429	19.936	18.506	0.300	0.766	0.655

$N_{Control}$ = 19; $N_{Concussed}$ = 16.

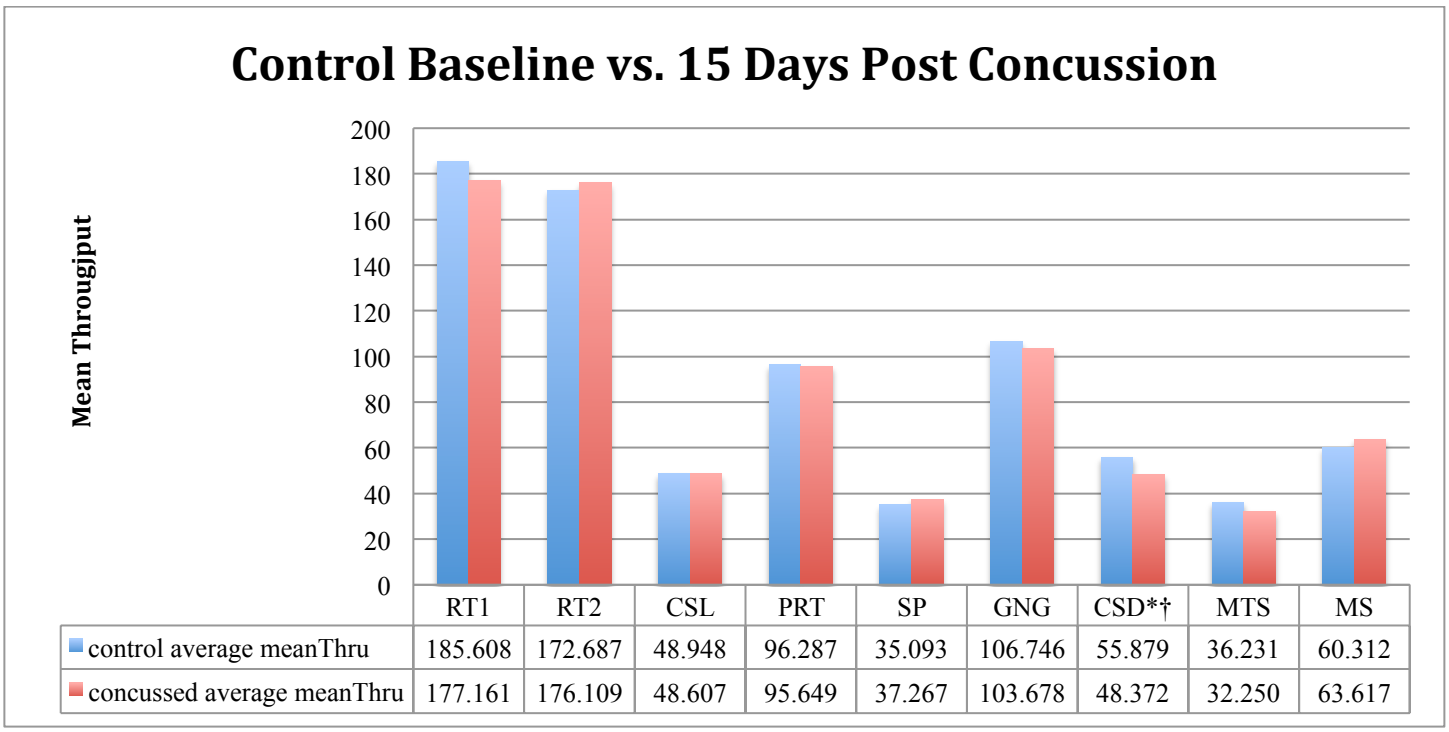


Table 7. Control Baselines vs. Concussed (15 Days Post Concussion): Mean Throughput.

	Control		Concussed		T-test Results			Wilcoxon
	meanThru (*M*)	meanThru (*SD*)	meanThru (*M*)	meanThru (*SD*)	*t* (*SD*)	*t*	*p*	*p*
RT1	185.608	29.594	177.161	29.404	29.514	0.813	0.423	0.455
RT2	172.687	30.439	176.109	24.952	28.268	-0.344	0.733	0.675
CSL	48.948	7.085	48.607	9.416	8.144	0.119	0.906	0.548
PRT	96.287	13.929	95.649	16.743	15.173	0.119	0.906	0.757
SP	35.093	7.200	37.267	6.087	6.755	-0.913	0.368	0.299
GNG	106.746	15.947	103.678	20.853	18.166	0.479	0.635	0.913
CSD	55.879	9.550	48.372	9.558	9.553	2.231	0.033	0.051
MTS	36.231	11.311	32.250	8.158	10.109	1.118	0.272	0.392
MS	60.312	17.224	63.617	22.985	19.845	-0.473	0.640	0.597

$N_{Control}$ = 19; $N_{Concussed}$ = 14.

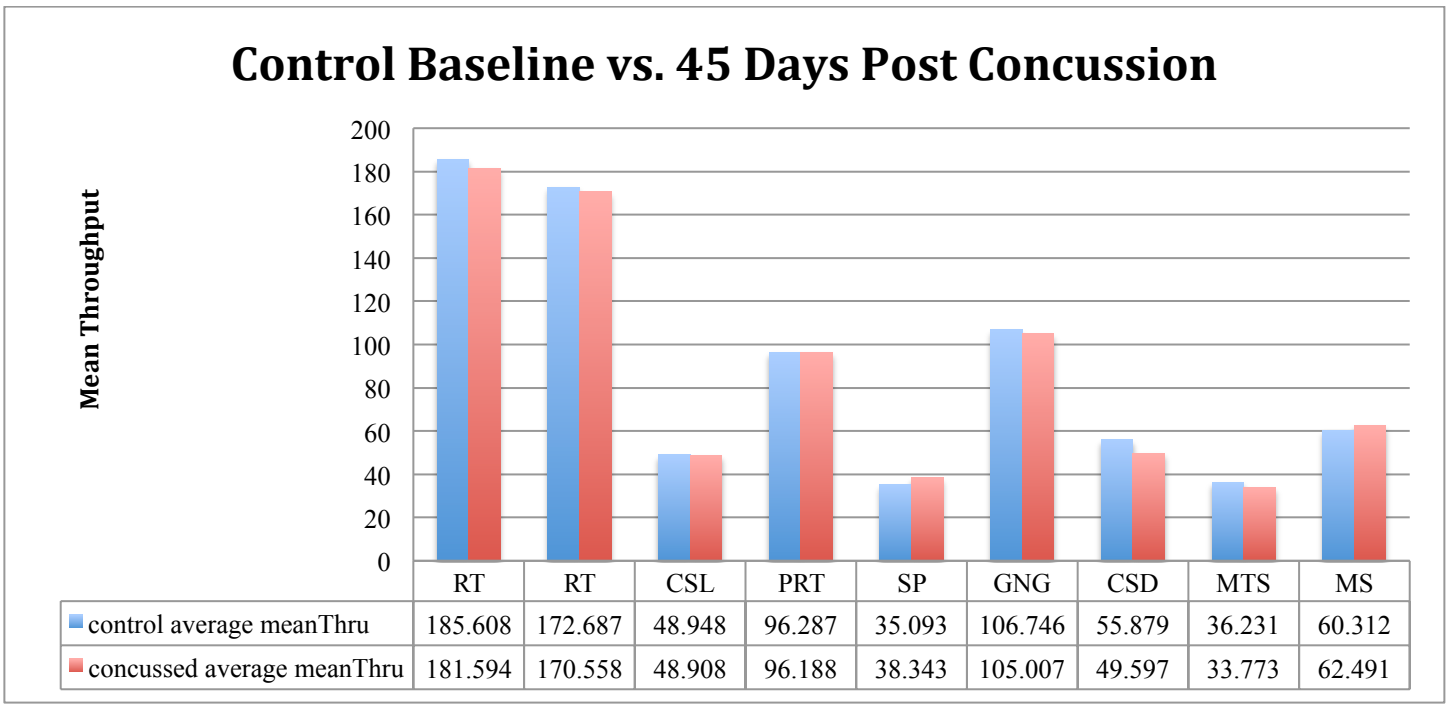


Table 8. Control Baselines vs. Concussed (45 Days Post Concussion): Mean Throughput.

	Control		Concussed		T-test Results			Wilcoxon
	meanThru (*M*)	meanThru (*SD*)	meanThru (*M*)	meanThru (*SD*)	*t* (*SD*)	*t*	*p*	*p*
RT1	185.608	29.594	181.594	19.232	26.592	0.386	0.702	0.614
RT2	172.687	30.439	170.558	20.539	27.538	0.198	0.845	0.836
CSL	48.948	7.085	48.908	7.117	7.096	0.015	0.988	0.801
PRT	96.287	13.929	96.188	13.584	13.815	0.018	0.986	0.836
SP	35.093	7.200	38.343	6.220	6.889	-1.207	0.238	0.113
GNG	106.746	15.947	105.007	17.569	16.505	0.270	0.789	0.801
CSD	55.879	9.550	49.597	13.770	11.135	1.444	0.160	0.302
MTS	36.231	11.311	33.773	6.763	10.027	0.627	0.536	0.909
MS	60.312	17.224	62.491	19.421	17.986	-0.310	0.759	0.836

$N_{Control}$ = 19; $N_{Concussed}$ = 10.

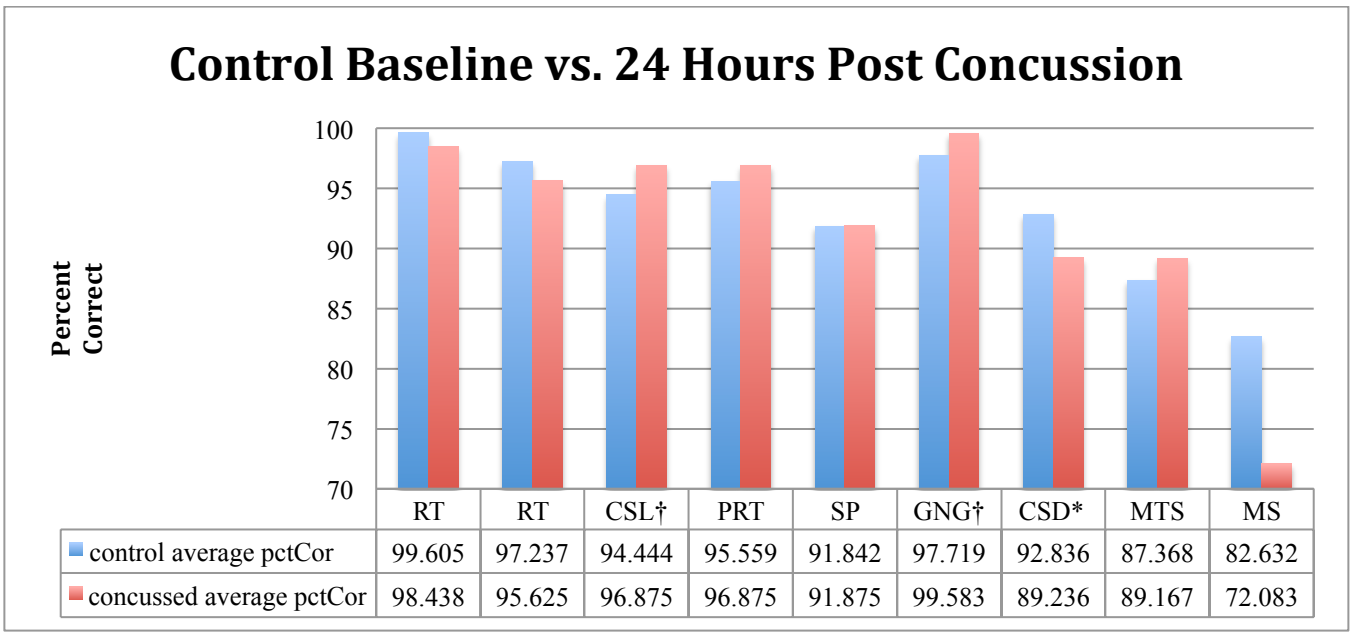


Table 9. Control Baselines vs. Concussed (24-hour Post Concussion): Percent Correct.

	Control		Concussed		T-test Results			Wilcoxon
	pctCor (*M*)	pctCor (*SD*)	pctCor (*M*)	pctCor (*SD*)	*t* (*SD*)	*t*	*p*	*p*
RT1	99.605	1.254	98.438	2.652	1.761	1.574	0.128	0.117
RT2	97.237	2.992	95.625	8.101	4.982	0.768	0.450	0.650
CSL	94.444	3.761	96.875	1.929	3.351	-1.721	0.098	0.132
PRT	95.559	3.346	96.875	2.362	3.102	-1.006	0.324	0.410
SP	91.842	7.305	91.875	3.720	6.504	-0.012	0.991	0.742
GNG	97.719	2.734	99.583	1.178	2.402	-1.841	0.077	0.083
CSD	92.836	6.164	89.236	3.128	5.486	1.557	0.132	0.028
MTS	87.368	9.912	89.167	6.607	9.108	-0.468	0.644	0.747
MS	82.632	19.894	72.083	34.638	24.918	1.004	0.325	0.979

$N_{Control}$ = 19; $N_{Concussed}$ = 8.

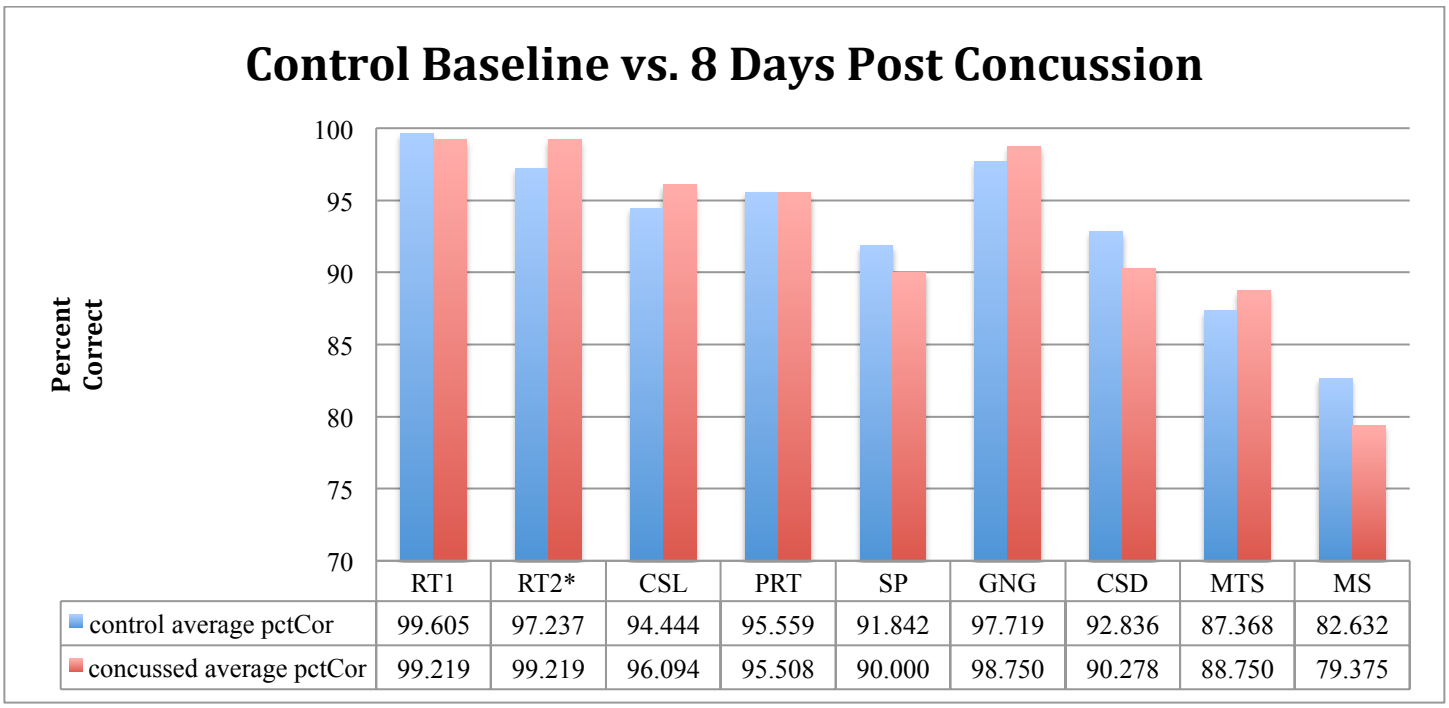


Table 10. Control Baselines vs. Concussed (8 Days Post Concussion): Percent Correct.

	Control		Concussed		T-test Results			Wilcoxon
	pctCor (*M*)	pctCor (*SD*)	pctCor (*M*)	pctCor (*SD*)	*t* (*SD*)	*t*	*p*	*p*
RT1	99.605	1.254	99.219	1.760	1.505	0.757	0.455	0.496
RT2	97.237	2.992	99.219	1.505	2.432	-2.402	0.022	0.029
CSL	94.444	3.761	96.094	3.295	3.557	-1.367	0.181	0.165
PRT	95.559	3.346	95.508	3.948	3.632	0.042	0.967	0.917
SP	91.842	7.305	90.000	7.303	7.304	0.743	0.463	0.423
GNG	97.719	2.734	98.750	1.667	2.311	-1.315	0.198	0.321
CSD	92.836	6.164	90.278	9.185	7.686	0.981	0.334	0.601
MTS	87.368	9.912	88.750	5.821	8.306	-0.490	0.627	0.933
MS	82.632	19.894	79.375	21.815	20.789	0.462	0.647	0.278

$N_{Control} = 19$; $N_{Concussed} = 16$.

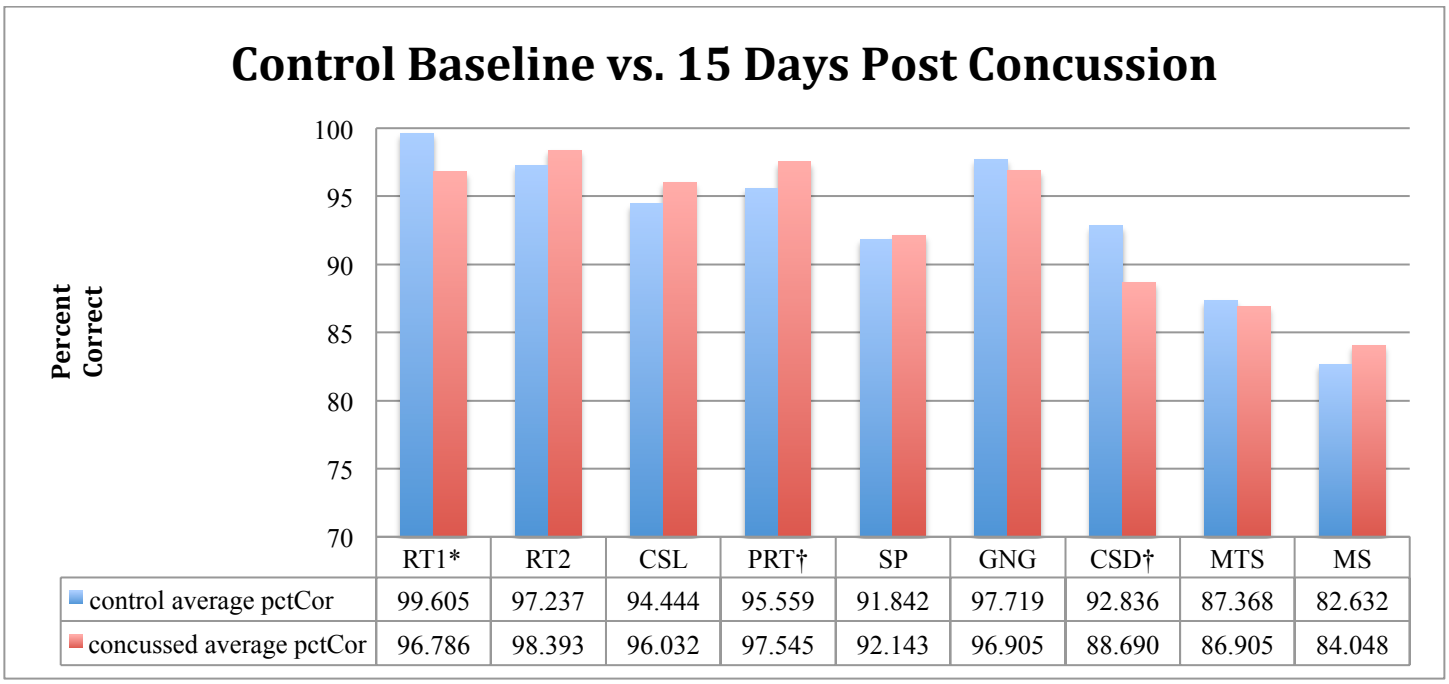


Table 11. Control Baselines vs. Concussed (15 Days Post Concussion): Percent Correct.

	Control		Concussed		T-test Results			Wilcoxon
	pctCor (*M*)	pctCor (*SD*)	pctCor (*M*)	pctCor (*SD*)	*t* (*SD*)	*t*	*p*	*p*
RT1	99.605	1.254	96.786	5.409	3.631	2.205	0.035	0.013
RT2	97.237	2.992	98.393	1.862	2.580	-1.272	0.213	0.321
CSL	94.444	3.761	96.032	3.307	3.578	-1.260	0.217	0.209
PRT	95.559	3.346	97.545	2.789	3.124	-1.804	0.081	0.065
SP	91.842	7.305	92.143	5.447	6.590	-0.130	0.898	0.895
GNG	97.719	2.734	96.905	6.976	4.974	0.465	0.645	0.656
CSD	92.836	6.164	88.690	7.585	6.796	1.732	0.093	0.105
MTS	87.368	9.912	86.905	6.467	8.636	0.152	0.880	0.671
MS	82.632	19.894	84.048	25.726	22.525	-0.178	0.859	0.658

$N_{Control}$ = 19; $N_{Concussed}$ = 14.

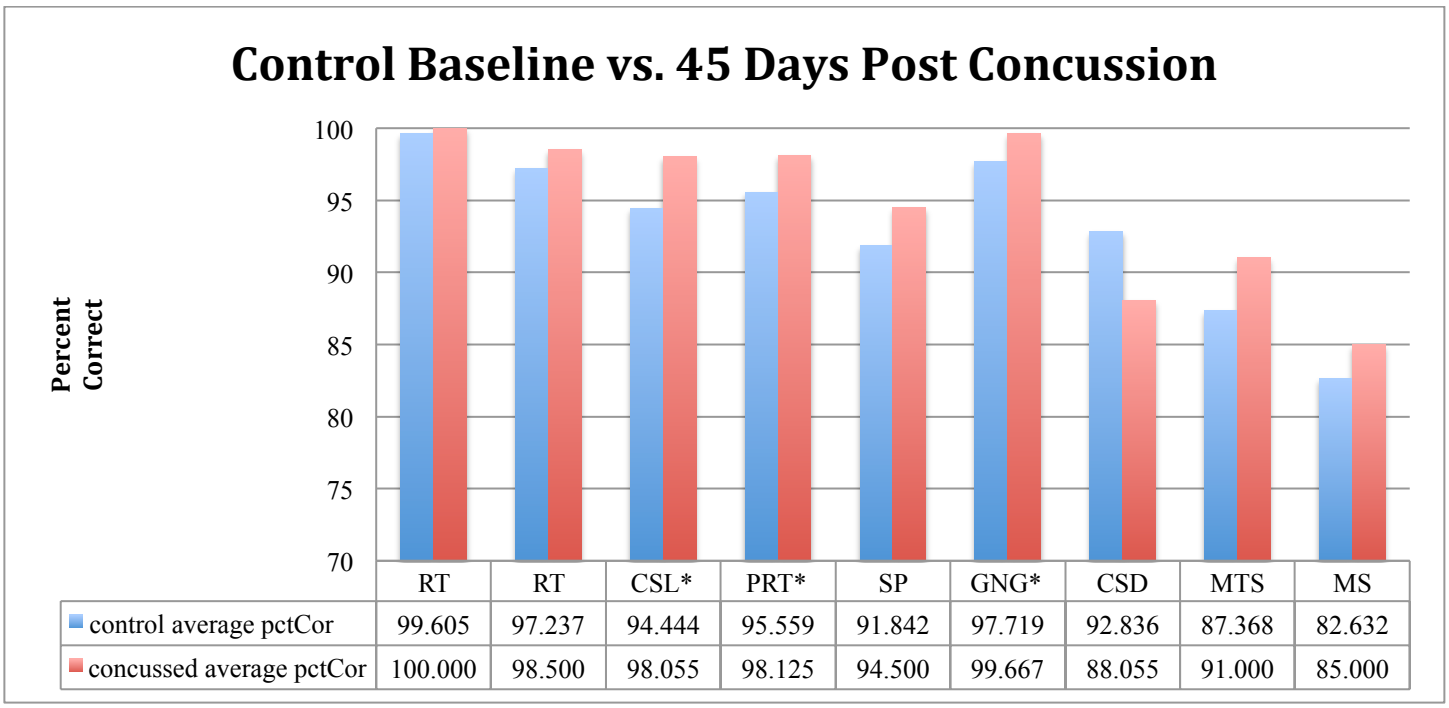


Table 12. Control Baselines vs. Concussed (45 Days Post Concussion): Percent Correct.

	Control		Concussed		T-test Results			Wilcoxon
	pctCor (*M*)	pctCor (*SD*)	pctCor (*M*)	pctCor (*SD*)	*t* (*SD*)	*t*	*p*	*p*
RT1	99.605	1.254	100.000	0.000	1.024	-0.987	0.332	0.321
RT2	97.237	2.992	98.500	1.748	2.644	-1.223	0.232	0.328
CSL	94.444	3.761	98.055	1.630	3.212	-2.878	0.008	0.005
PRT	95.559	3.346	98.125	2.185	3.009	-2.183	0.038	0.036
SP	91.842	7.305	94.500	4.378	6.478	-1.050	0.303	0.471
GNG	97.719	2.734	99.667	1.054	2.313	-2.155	0.040	0.044
CSD	92.836	6.164	88.055	13.737	9.393	1.303	0.204	0.483
MTS	87.368	9.912	91.000	5.676	8.731	-1.065	0.296	0.468
MS	82.632	19.894	85.000	15.336	18.500	-0.328	0.746	0.693

$N_{Control} = 19$; $N_{Concussed} = 10$.

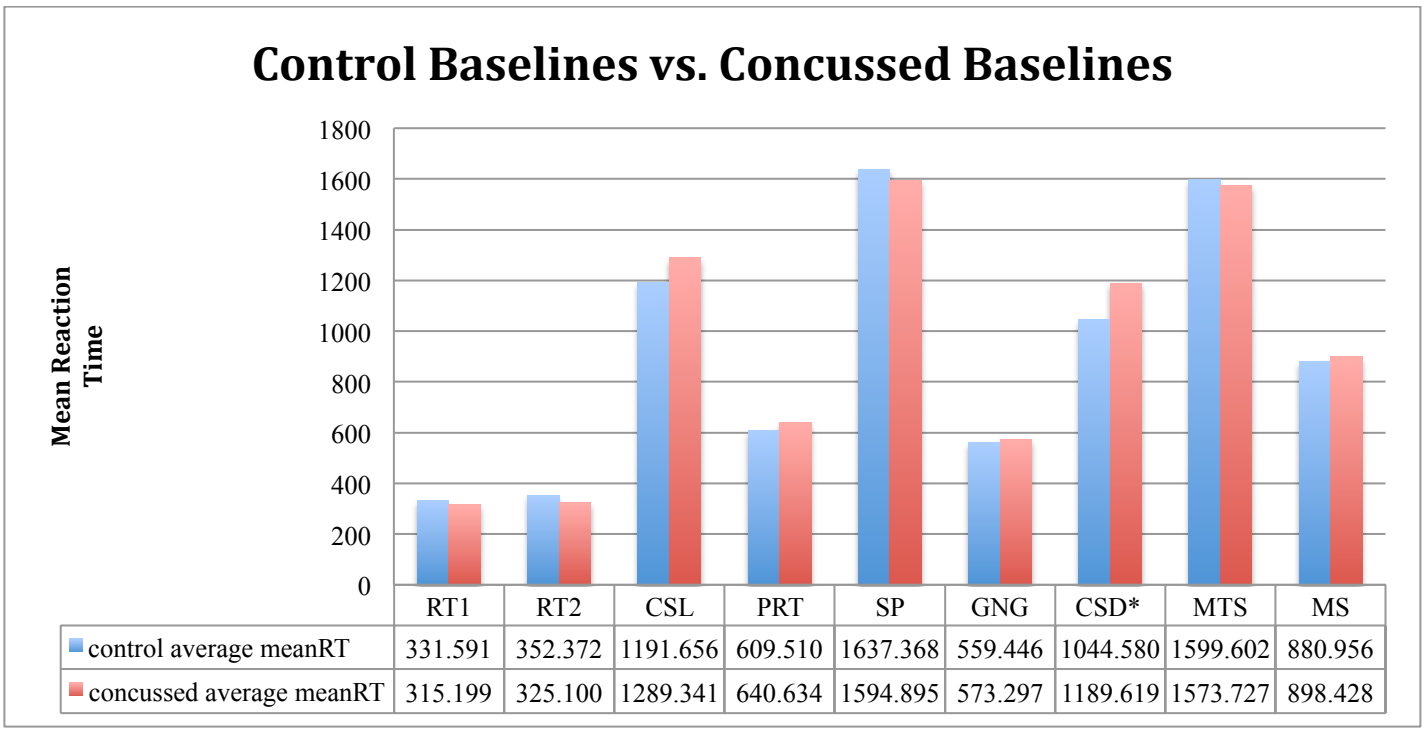


Table 13. Control At Baselines vs. Concussed At Baseline: Mean Reaction Time.

	Control		Concussed		T-test Results			Wilcoxon
	meanRT (*M*)	meanRT (*SD*)	meanRT (*M*)	meanRT (*SD*)	*t* (*SD*)	*t*	*p*	*p*
RT1	331.591	60.778	315.199	34.927	48.598	1.077	0.288	0.705
RT2	352.372	64.683	325.100	42.253	53.780	1.619	0.113	0.187
CSL	1191.656	209.185	1289.341	302.398	263.506	-1.184	0.244	0.278
PRT	609.510	96.054	640.634	98.343	97.293	-1.021	0.313	0.255
SP	1637.368	349.335	1594.895	285.083	316.363	0.429	0.671	0.666
GNG	559.446	88.338	573.297	141.875	120.167	-0.368	0.715	0.705
CSD	1044.580	185.994	1189.619	225.441	208.166	-2.225	0.032	0.025
MTS	1599.602	368.970	1573.727	295.950	331.655	0.249	0.805	0.724
MS	880.956	158.446	898.428	228.783	199.427	-0.280	0.781	0.824

$N_{Control}$ = 19; $N_{Concussed}$ = 22.

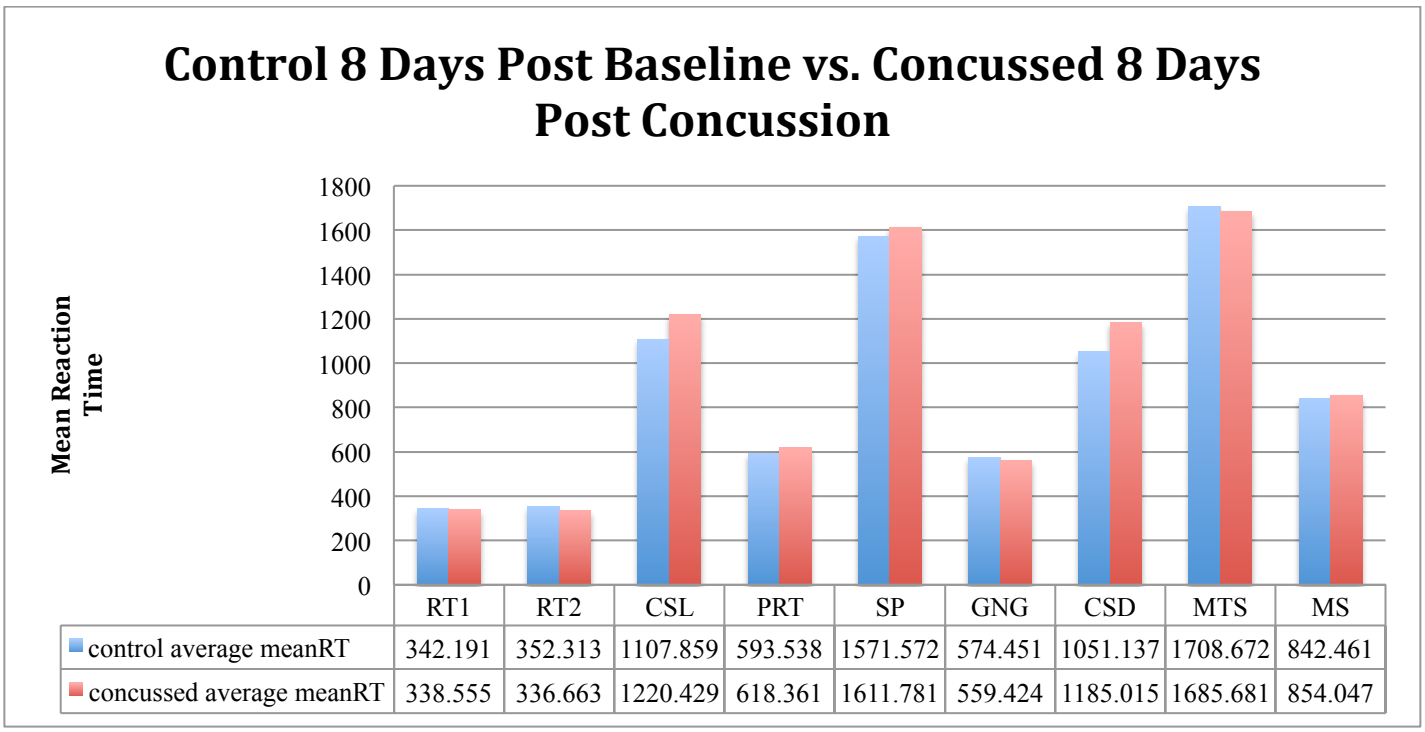


Table 14. Control 8 Days Post Baseline vs. Concussed 8 Days Post Concussion: Mean Reaction Time.

	Control		Concussed		T-test Results			Wilcoxon
	meanRT (*M*)	meanRT (*SD*)	meanRT (*M*)	meanRT (*SD*)	*t* (*SD*)	*t*	*p*	*p*
RT1	342.191	83.778	338.555	52.533	70.868	0.149	0.882	0.523
RT2	352.313	65.231	336.663	44.591	56.503	0.806	0.426	0.629
CSL	1107.859	190.638	1220.429	223.772	206.832	-1.584	0.123	0.133
PRT	593.538	103.429	618.361	90.298	97.495	-0.741	0.464	0.277
SP	1571.572	357.599	1611.781	354.023	355.928	-0.329	0.744	0.641
GNG	574.451	103.566	559.424	90.291	97.568	0.448	0.657	0.769
CSD	1051.137	173.883	1185.015	344.811	267.945	-1.454	0.156	0.479
MTS	1708.672	383.430	1685.681	329.130	359.001	0.186	0.853	1.000
MS	842.461	213.938	854.047	259.578	236.431	-0.143	0.887	0.904

$N_{Control}$ = 18; $N_{Concussed}$ = 16.

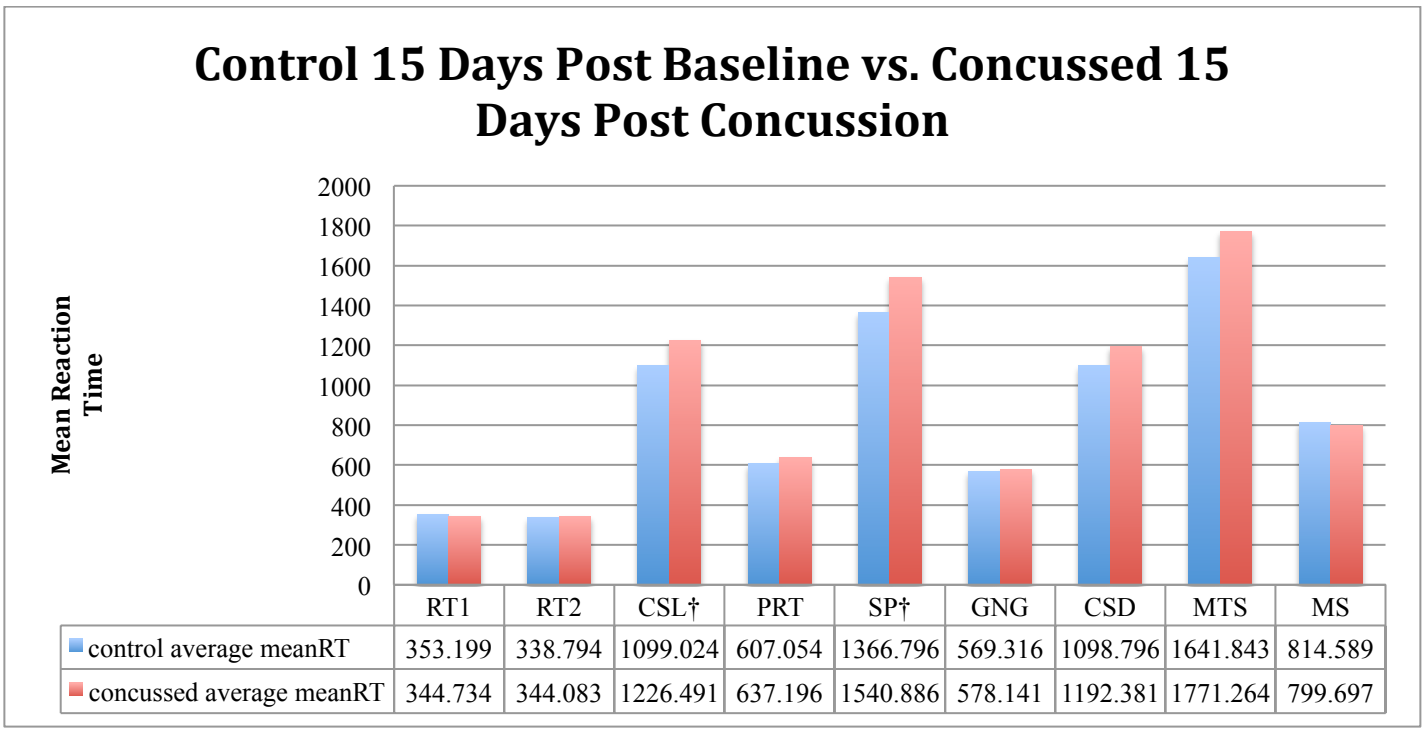


Table 15. Control 15 Days Post Baseline vs. Concussed 15 Days Post Concussion: Mean Reaction Time.

	Control		Concussed		T-test Results			Wilcoxon
	meanRT (*M*)	meanRT (*SD*)	meanRT (*M*)	meanRT (*SD*)	*t* (*SD*)	*t*	*p*	*p*
RT1	353.199	83.496	344.734	71.621	77.785	0.288	0.776	0.872
RT2	338.794	32.738	344.083	47.847	40.994	-0.341	0.736	0.982
CSL	1099.024	144.133	1226.491	208.422	179.184	-1.882	0.071	0.051
PRT	607.054	156.075	637.196	154.840	155.459	-0.513	0.612	0.346
SP	1366.796	248.196	1540.886	276.292	262.620	-1.754	0.091	0.113
GNG	569.316	104.213	578.141	111.317	107.824	-0.217	0.830	0.909
CSD	1098.796	224.184	1192.381	255.468	240.335	-1.030	0.312	0.535
MTS	1641.843	257.690	1771.264	408.165	341.323	-1.003	0.325	0.395
MS	814.589	159.596	799.697	218.689	191.436	0.206	0.839	0.765

$N_{Control}$ = 14; $N_{Concussed}$ = 14.

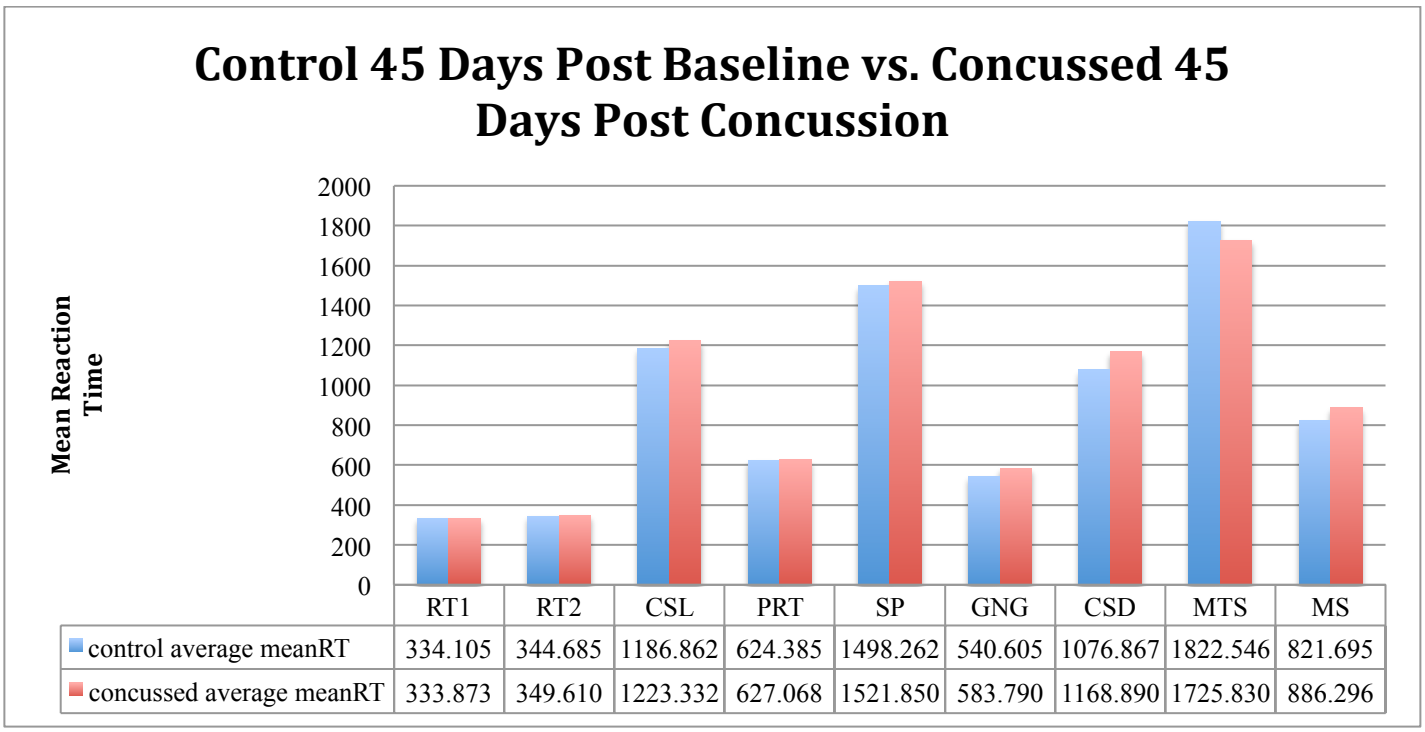


Table 16. Control 45 Days Post Baseline vs. Concussed 45 Days Post Concussion: Mean Reaction Time.

	Control		Concussed		T-test Results			Wilcoxon
	meanRT (*M*)	meanRT (*SD*)	meanRT (*M*)	meanRT (*SD*)	*t* (*SD*)	*t*	*p*	*p*
RT1	334.105	42.655	333.873	36.570	40.160	0.014	0.989	0.975
RT2	344.685	78.532	349.610	38.211	64.420	-0.182	0.858	0.733
CSL	1186.862	213.711	1223.332	169.054	195.823	-0.443	0.662	0.687
PRT	624.385	96.509	627.068	106.451	100.890	-0.063	0.950	0.926
SP	1498.262	335.106	1521.850	239.655	297.967	-0.188	0.853	0.687
GNG	540.605	84.207	583.790	95.360	89.157	-1.152	0.262	0.369
CSD	1076.867	184.891	1168.890	293.503	237.598	-0.921	0.368	0.687
MTS	1822.546	275.655	1725.830	269.019	272.830	0.843	0.409	0.515
MS	821.695	177.843	886.296	153.209	167.729	-0.916	0.370	0.369

$N_{Control}$ = 13; $N_{Concussed}$ = 10.

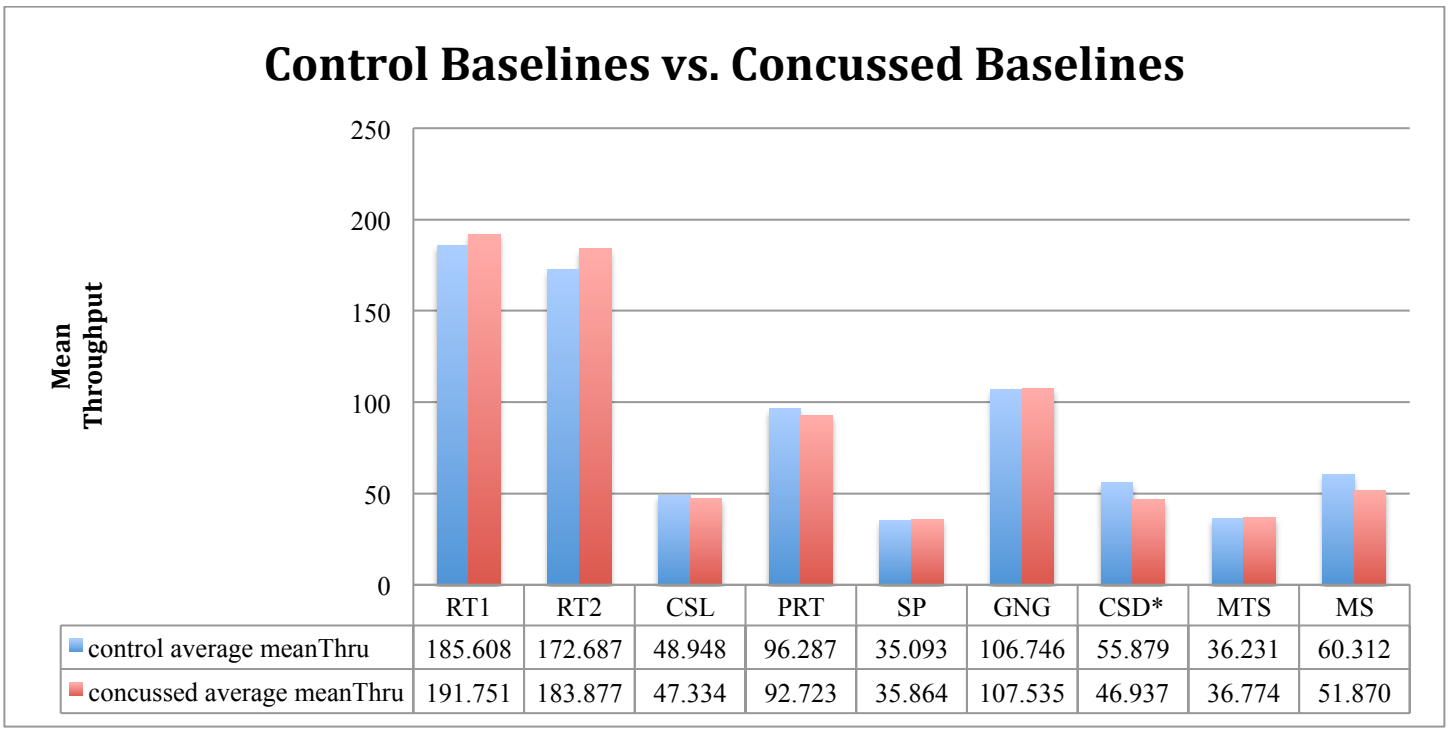


Table 17. Control At Baselines vs. Concussed At Baseline: Mean Throughput.

	Control		Concussed		T-test Results			Wilcoxon
	meanThru (*M*)	meanThru (*SD*)	meanThru (*M*)	meanThru (*SD*)	*t* (*SD*)	*t*	*p*	*p*
RT1	185.608	29.594	191.751	19.709	24.766	-0.792	0.433	0.705
RT2	172.687	30.439	183.877	24.805	27.549	-1.297	0.202	0.245
CSL	48.948	7.085	47.334	11.535	9.737	0.529	0.600	0.505
PRT	96.287	13.929	92.723	13.523	13.712	0.830	0.412	0.395
SP	35.093	7.200	35.864	6.453	6.808	-0.361	0.720	0.629
GNG	106.746	15.947	107.535	20.243	18.385	-0.137	0.892	0.456
CSD	55.879	9.550	46.937	9.132	9.327	3.061	0.004	0.003
MTS	36.231	11.311	36.774	7.458	9.434	-0.184	0.855	0.255
MS	60.312	17.224	51.870	18.606	17.981	1.499	0.142	0.178

$N_{Control}$ = 19; $N_{Concussed}$ = 22.

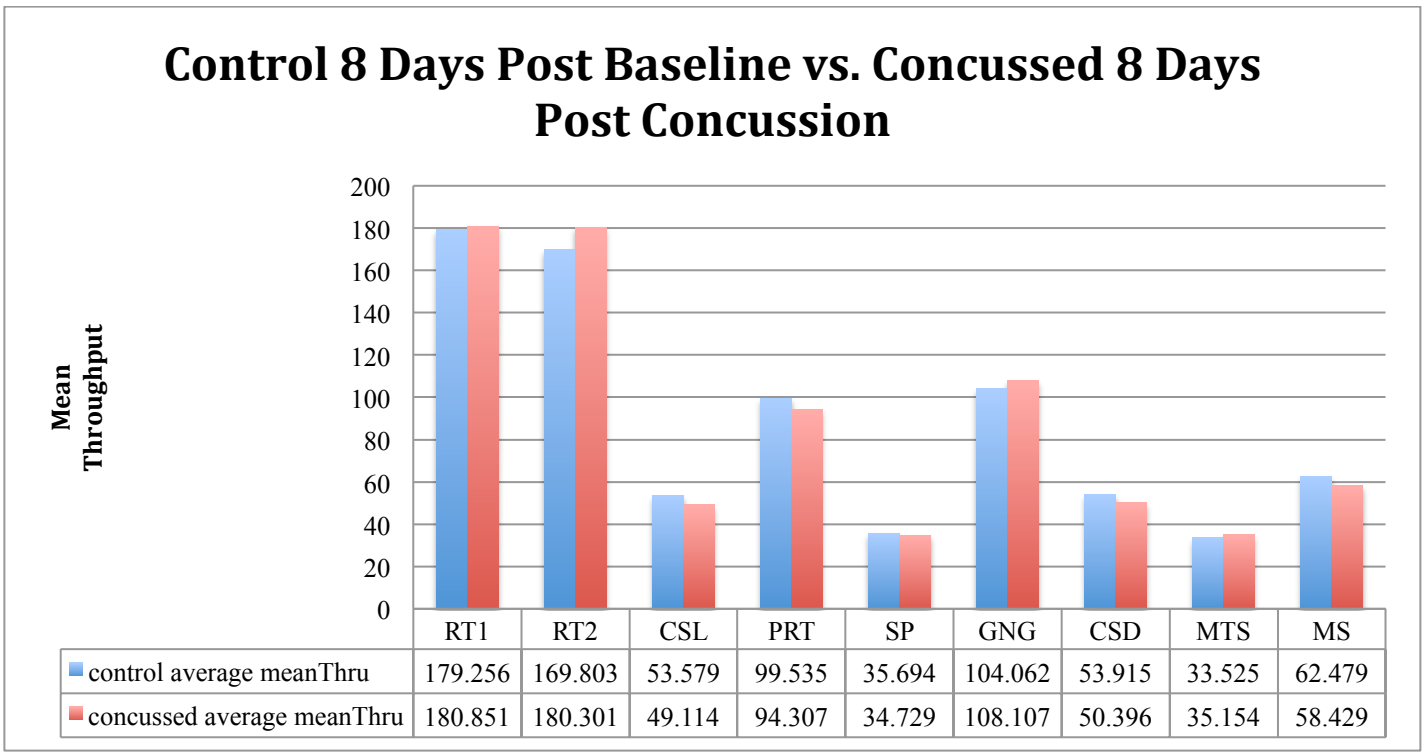


Table 18. Control 8 Days Post Baseline vs. Concussed 8 Days Post Concussion: Mean Throughput.

	Control		Concussed		T-test Results			Wilcoxon
	meanThru (*M*)	meanThru (*SD*)	meanThru (*M*)	meanThru (*SD*)	*t* (*SD*)	*t*	*p*	*p*
RT1	179.256	32.657	180.851	26.936	30.111	-0.154	0.878	0.593
RT2	169.803	31.585	180.301	22.940	27.869	-1.096	0.281	0.334
CSL	53.579	9.513	49.114	9.357	9.440	1.376	0.178	0.196
PRT	99.535	14.138	94.307	12.687	13.477	1.129	0.267	0.343
SP	35.694	6.107	34.729	5.938	6.028	0.466	0.644	0.617
GNG	104.062	18.034	108.107	17.424	17.751	-0.663	0.512	0.593
CSD	53.915	7.239	50.396	13.652	10.733	0.954	0.347	0.743
MTS	33.525	8.737	35.154	7.657	8.248	-0.575	0.569	0.717
MS	62.479	17.405	58.429	19.936	18.634	0.633	0.532	0.641

$N_{Control} = 18$; $N_{Concussed} = 16$.

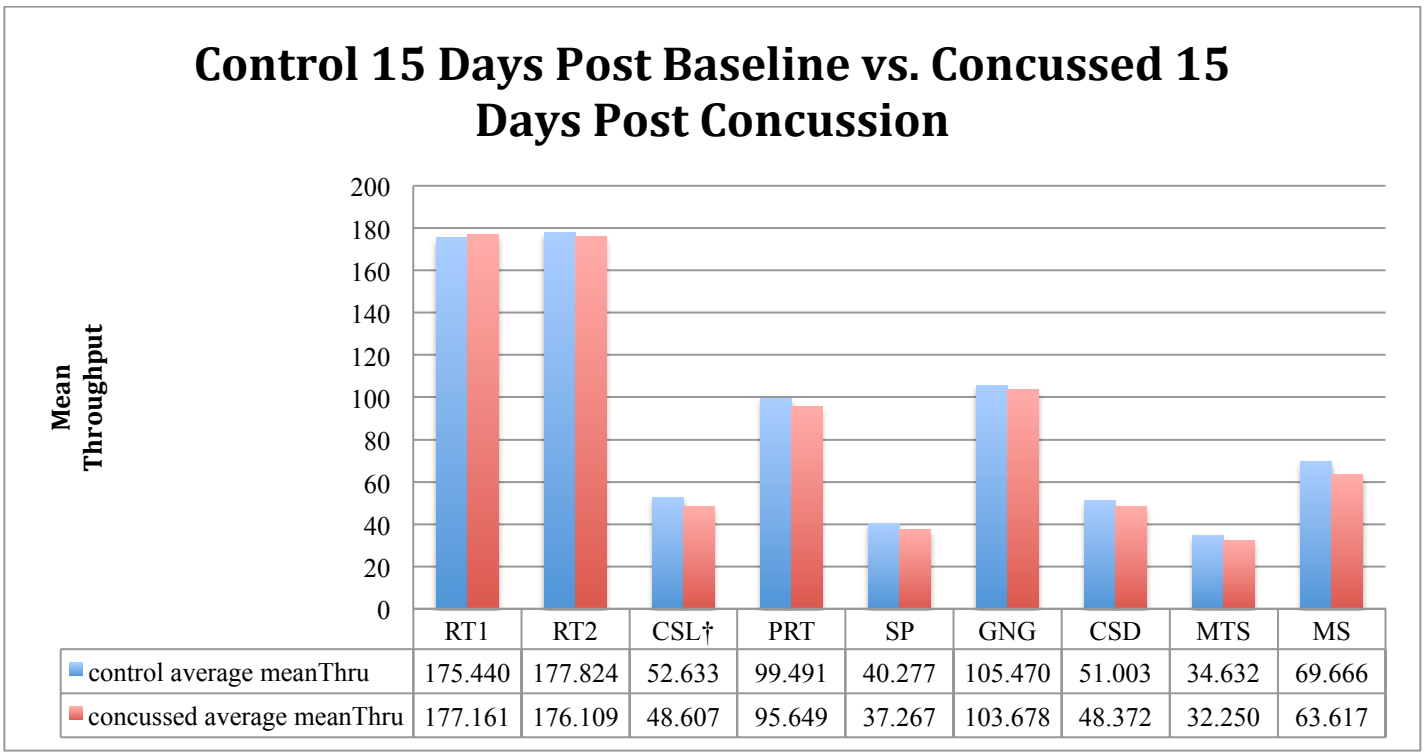


Table 19. Control 15 Days Post Baseline vs. Concussed 15 Days Post Concussion: Mean Throughput.

	Control		Concussed		T-test Results			Wilcoxon
	meanThru (*M*)	meanThru (*SD*)	meanThru (*M*)	meanThru (*SD*)	*t* (*SD*)	*t*	*p*	*p*
RT1	175.440	32.670	177.161	29.404	31.080	-0.147	0.885	0.872
RT2	177.824	18.240	176.109	24.952	21.855	0.208	0.837	0.909
CSL	52.633	5.999	48.607	9.416	7.895	1.349	0.189	0.085
PRT	99.491	19.564	95.649	16.743	18.208	0.558	0.581	0.662
SP	40.277	8.468	37.267	6.087	7.374	1.080	0.290	0.448
GNG	105.470	23.690	103.678	20.853	22.316	0.212	0.833	0.909
CSD	51.003	10.521	48.372	9.558	10.051	0.693	0.495	0.535
MTS	34.632	4.928	32.250	8.158	6.739	0.935	0.358	0.190
MS	69.666	14.139	63.617	22.985	19.082	0.839	0.409	0.535

$N_{Control} = 14$; $N_{Concussed} = 14$.

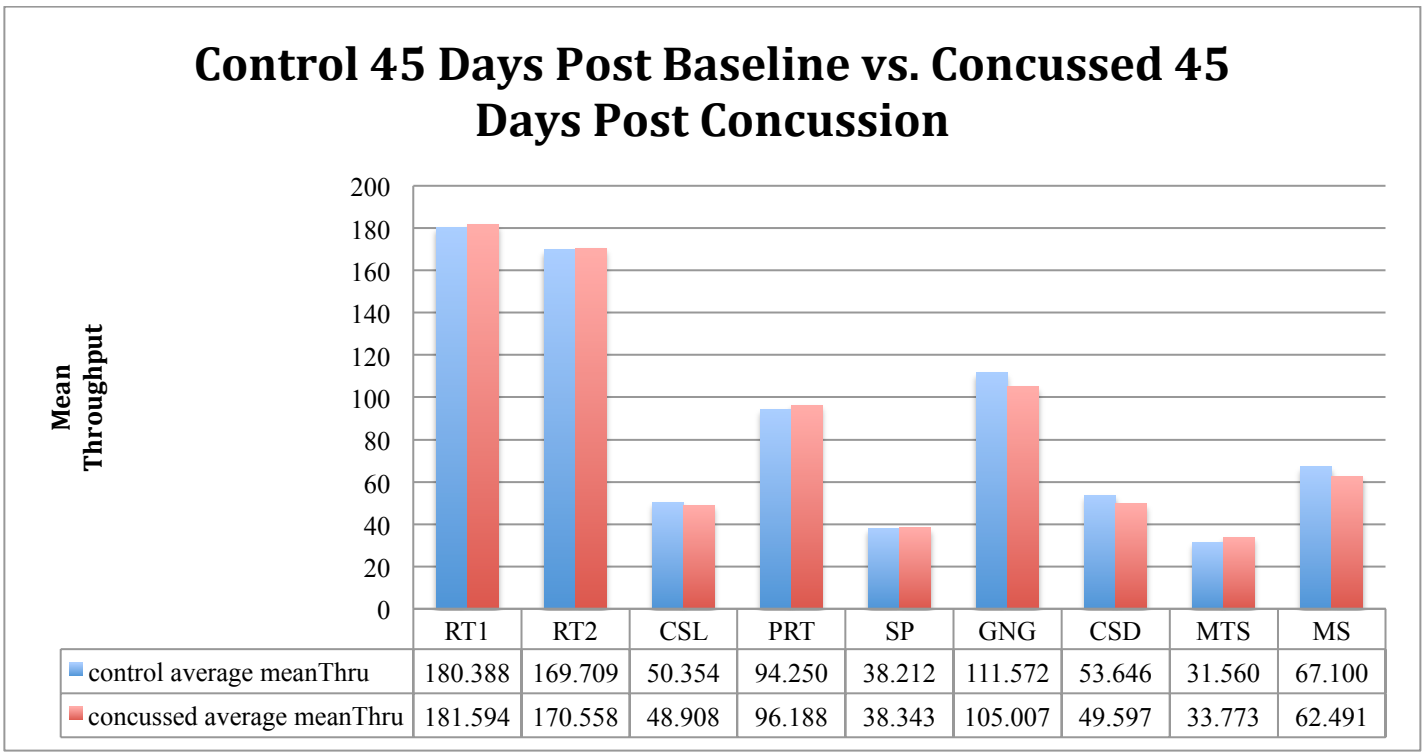


Table 20. Control 45 Days Post Baseline vs. Concussed 45 Days Post Concussion: Mean Throughput.

	Control		Concussed		T-test Results			Wilcoxon
	meanThru (*M*)	meanThru (*SD*)	meanThru (*M*)	meanThru (*SD*)	*t* (*SD*)	*t*	*p*	*p*
RT1	180.388	22.648	181.594	19.232	21.251	-0.135	0.894	0.780
RT2	169.709	32.349	170.558	20.539	27.906	-0.072	0.943	0.877
CSL	50.354	8.904	48.908	7.117	8.186	0.420	0.679	0.828
PRT	94.250	15.107	96.188	13.584	14.474	-0.318	0.753	0.642
SP	38.212	9.430	38.343	6.220	8.209	-0.038	0.970	0.975
GNG	111.572	16.964	105.007	17.569	17.226	0.906	0.375	0.476
CSD	53.646	8.388	49.597	13.770	11.021	0.873	0.392	0.687
MTS	31.560	5.775	33.773	6.763	6.218	-0.846	0.407	0.369
MS	67.100	20.340	62.491	19.421	19.951	0.549	0.589	0.598

$N_{Control} = 13$; $N_{Concussed} = 10$.

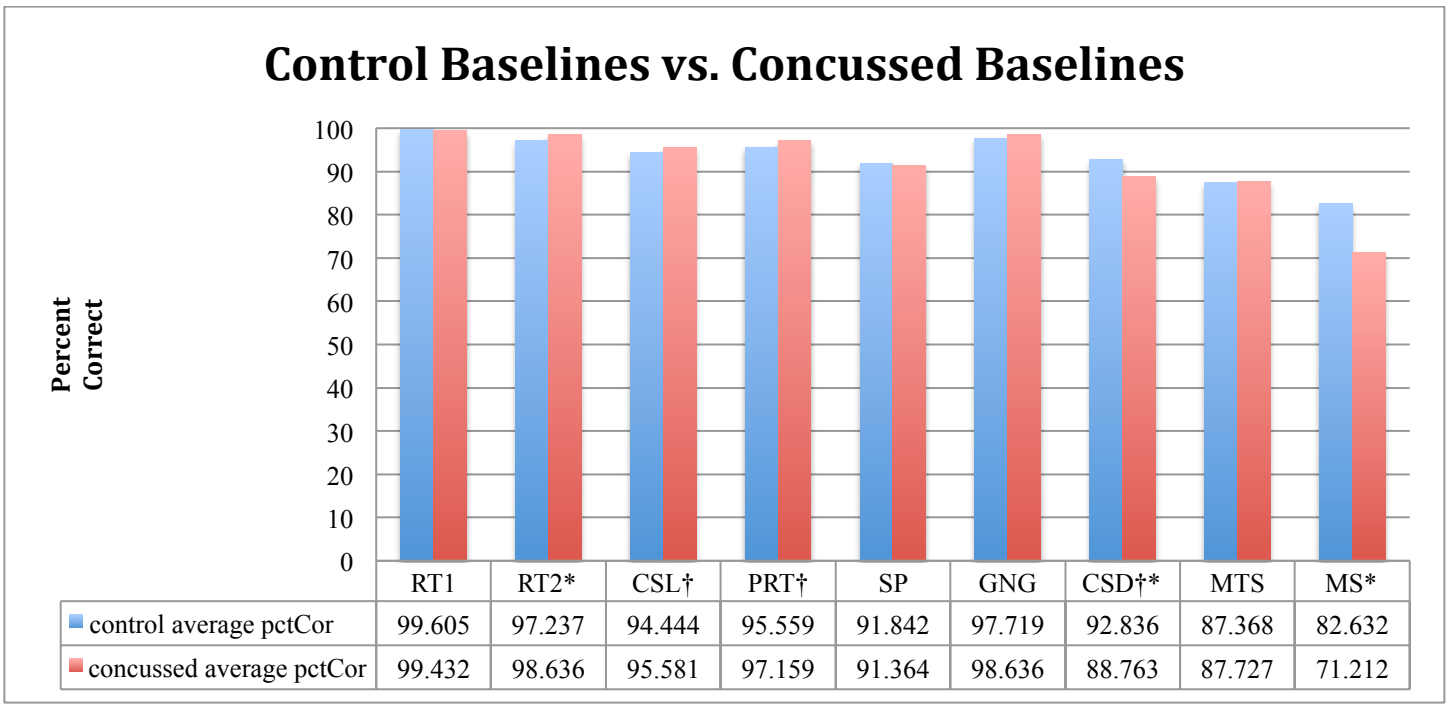


Table 21. Control At Baselines vs. Concussed At Baseline: Percent Correct.

	Control		Concussed		T-test Results			Wilcoxon
	pctCor (*M*)	pctCor (*SD*)	pctCor (*M*)	pctCor (*SD*)	*t* (*SD*)	*t*	*p*	*p*
RT1	99.605	1.254	99.432	1.321	1.290	0.429	0.670	0.537
RT2	97.237	2.992	98.636	3.060	3.029	-1.475	0.148	0.042
CSL	94.444	3.761	95.581	4.488	4.168	-0.871	0.389	0.090
PRT	95.559	3.346	97.159	2.535	2.937	-1.739	0.090	0.112
SP	91.842	7.305	91.364	6.207	6.736	0.227	0.822	0.715
GNG	97.719	2.734	98.636	2.220	2.471	-1.185	0.243	0.266
CSD	92.836	6.164	88.763	7.298	6.798	1.913	0.063	0.039
MTS	87.368	9.912	87.727	8.254	9.057	-0.126	0.900	0.979
MS	82.632	19.894	71.212	23.266	21.775	1.675	0.102	0.048

$N_{Control}$ = 19; $N_{Concussed}$ = 22.

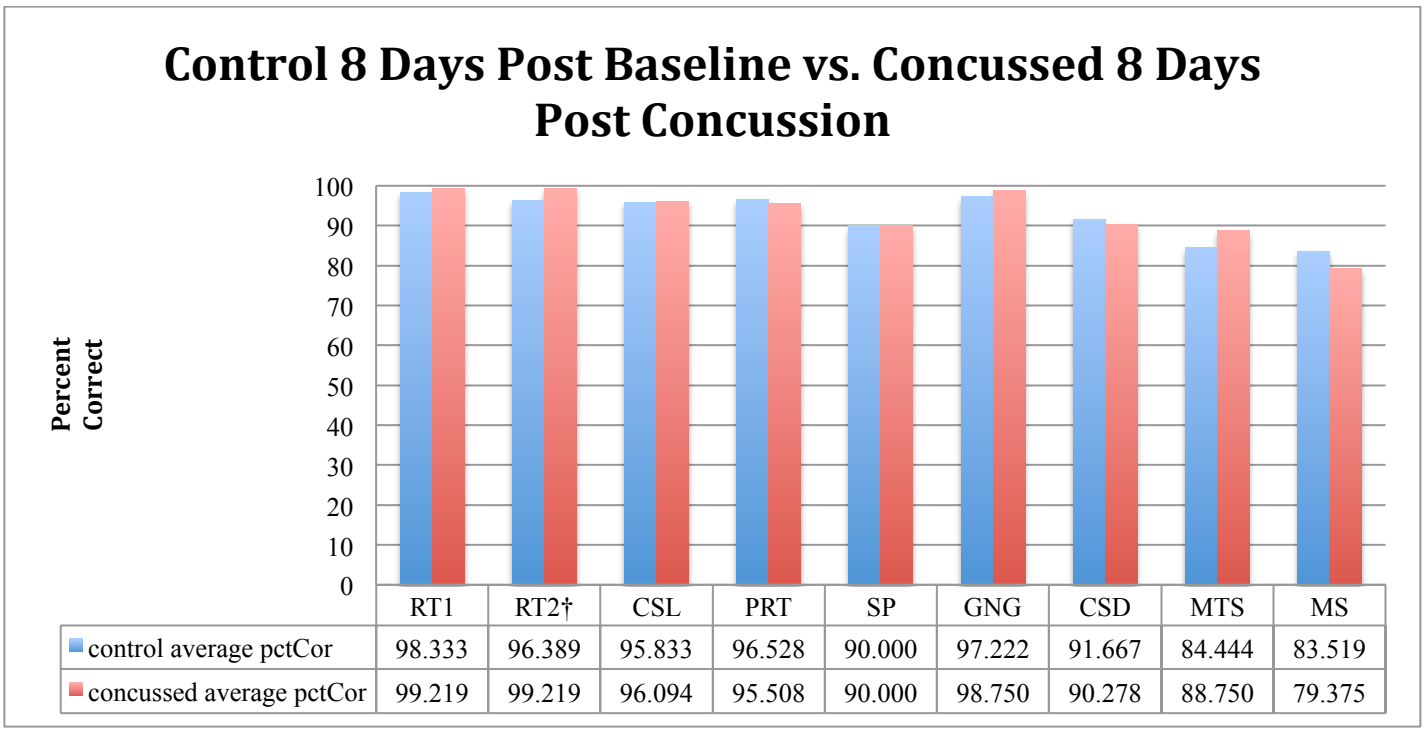


Table 22. Control 8 Days Post Baseline vs. Concussed 8 Days Post Concussion: Mean Throughput.

	Control		Concussed		T-test Results			Wilcoxon
	pctCor (*M*)	pctCor (*SD*)	pctCor (*M*)	pctCor (*SD*)	*t* (*SD*)	*t*	*p*	*p*
RT1	98.333	3.321	99.219	1.760	2.704	-0.953	0.348	0.643
RT2	96.389	6.314	99.219	1.505	4.716	-1.746	0.090	0.134
CSL	95.833	2.382	96.094	3.295	2.847	-0.266	0.792	0.540
PRT	96.528	3.196	95.508	3.948	3.568	0.832	0.412	0.487
SP	90.000	7.859	90.000	7.303	7.603	0.000	1.000	0.986
GNG	97.222	3.477	98.750	1.667	2.779	-1.600	0.119	0.253
CSD	91.667	8.784	90.278	9.185	8.974	0.450	0.655	0.807
MTS	84.444	11.547	88.750	5.821	9.312	-1.346	0.188	0.328
MS	83.519	17.950	79.375	21.815	19.855	0.607	0.548	0.578

$N_{Control}$ = 18; $N_{Concussed}$ = 16.

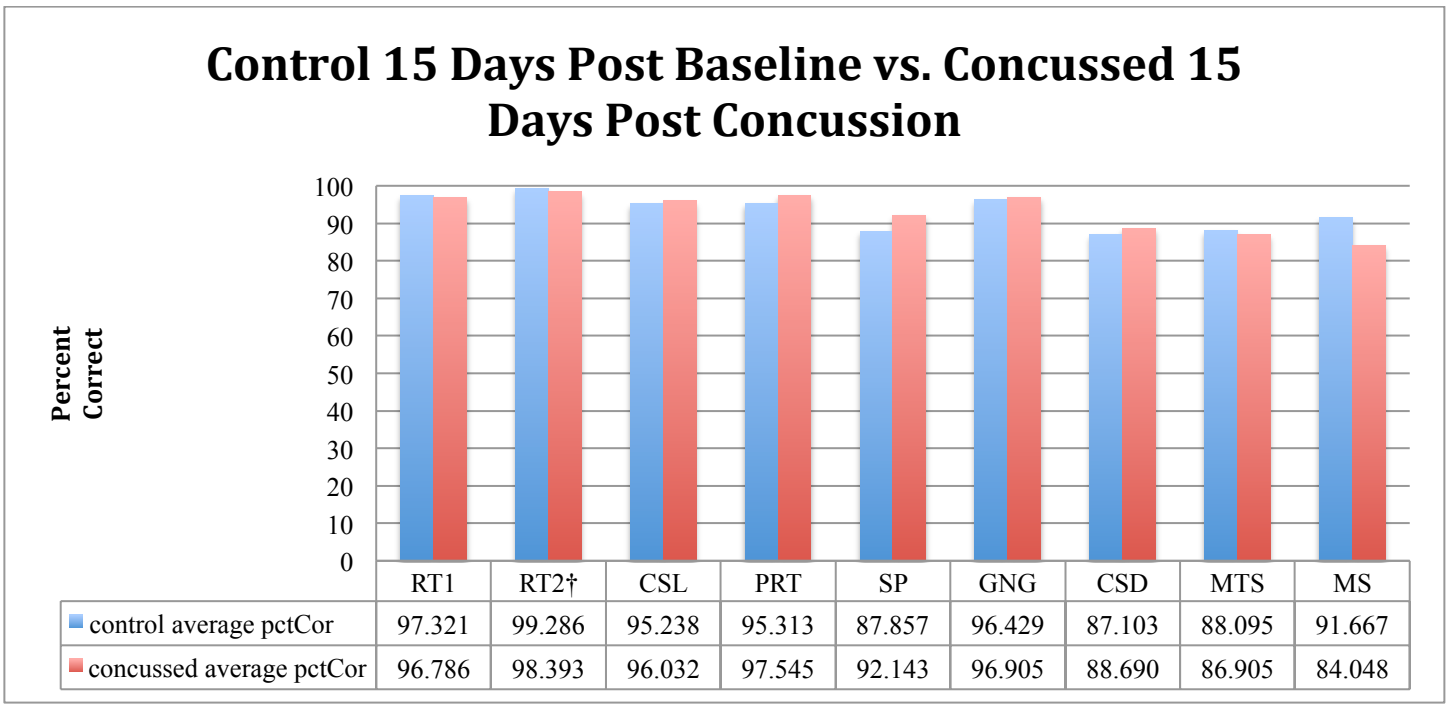


Table 23. Control 15 Days Post Baseline vs. Concussed 15 Days Post Concussion: Mean Throughput.

	Control		Concussed		T-test Results			Wilcoxon
	pctCor (*M*)	pctCor (*SD*)	pctCor (*M*)	pctCor (*SD*)	*t* (*SD*)	*t*	*p*	*p*
RT1	97.321	4.750	96.786	5.409	5.090	0.278	0.783	0.591
RT2	99.286	2.064	98.393	1.862	1.966	1.202	0.240	0.074
CSL	95.238	4.954	96.032	3.307	4.212	-0.498	0.622	1.000
PRT	95.313	4.707	97.545	2.789	3.869	-1.526	0.139	0.184
SP	87.857	8.926	92.143	5.447	7.394	-1.534	0.137	0.166
GNG	96.429	6.976	96.905	6.976	6.976	-0.181	0.858	0.663
CSD	87.103	9.025	88.690	7.585	8.336	-0.504	0.619	0.746
MTS	88.095	3.125	86.905	6.467	5.079	0.620	0.541	0.867
MS	91.667	16.317	84.048	25.726	21.542	0.936	0.358	0.153

$N_{Control} = 14$; $N_{Concussed} = 14$.

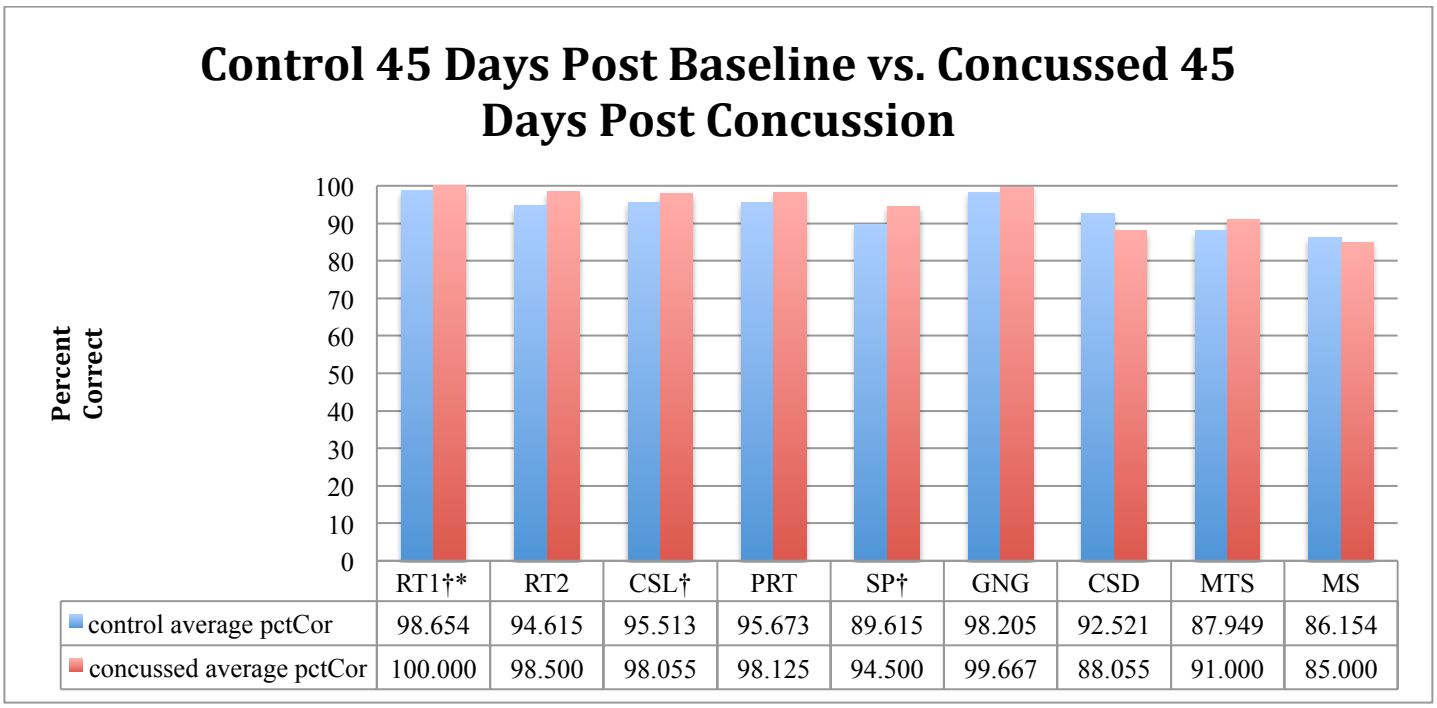


Table 24. Control 45 Days Post Baseline vs. Concussed 45 Days Post Concussion: Mean Throughput.

	Control		Concussed		T-test Results			Wilcoxon
	pctCor (*M*)	pctCor (*SD*)	pctCor (*M*)	pctCor (*SD*)	*t* (*SD*)	*t*	*p*	*p*
RT1	98.654	2.193	100.000	0.000	1.657	-1.931	0.067	0.034
RT2	94.615	11.173	98.500	1.748	8.523	-1.084	0.291	1.000
CSL	95.513	4.211	98.055	1.630	3.357	-1.800	0.086	0.173
PRT	95.673	4.864	98.125	2.185	3.946	-1.477	0.154	0.263
SP	89.615	7.206	94.500	4.378	6.155	-1.887	0.073	0.074
GNG	98.205	3.225	99.667	1.054	2.533	-1.372	0.185	0.228
CSD	92.521	7.117	88.055	13.737	10.479	1.013	0.322	0.490
MTS	87.949	7.010	91.000	5.676	6.472	-1.121	0.275	0.285
MS	86.154	18.250	85.000	15.336	17.062	0.161	0.874	0.730

$N_{Control} = 13$; $N_{Concussed} = 10$.

Baseline (controls) vs. 24-hour (concussed)								
	meanRT							
	Controls			Concussed				
	N	*M*	*SD*	*N*	*M*	*SD*	*p*	*t*
RT1	26	327.866	55.304	18	345.772	64.197	0.328	-0.989
CSL1	26	1207.597	234.592	18	1244.743	246.673	0.616	-0.506
PRT1	26	619.007	108.165	18	625.028	85.165	0.845	-0.197
SP1	26	1706.992	355.904	18	1689.939	328.314	0.873	0.161
GNG1	26	539.972	63.228	18	571.193	94.926	0.197	-1.312
CSD2	26	1074.090	187.137	18	1120.066	254.494	0.493	-0.691
MTS1	26	1667.365	261.038	18	1668.200	263.130	0.992	-0.010
MS1	26	910.263	220.549	18	847.723	209.511	0.351	0.944
RT2	26	345.570	39.562	18	346.808	52.982	0.930	-0.089

There are no significant differences in any of the DANA subtests for mean reaction time between baselines for controls and 24-hour assessments of concussed athletes.

Baseline (controls) vs. 8 Day (concussed)								
	meanRT							
	Controls			Concussed				
	N	*M*	*SD*	*N*	*M*	*SD*	*p*	*t*
RT1	26	327.866	55.304	18	334.701	50.630	0.679	-0.417
CSL1	26	1207.597	234.592	18	1191.663	236.205	0.826	0.221
PRT1	26	619.007	108.165	18	608.993	90.577	0.749	0.322
SP1	26	1706.992	355.904	18	1576.978	348.014	0.236	1.202
GNG1	26	539.972	63.228	18	546.994	92.239	0.766	-0.300
CSD2	26	1074.090	187.137	18	1147.413	341.915	0.365	-0.916
MTS1	26	1667.365	261.038	18	1657.517	320.309	0.911	0.112
MS1	26	910.263	220.549	18	837.283	248.673	0.312	1.024
RT2	26	345.570	39.562	18	333.846	42.682	0.355	0.936

There are no significant differences in any of the DANA subtests for mean reaction time between baselines for controls and assessments 8 days after concussion for concussed athletes.

Baseline (controls) vs. 15 Day (concussed)								
	meanRT							
	Controls			Concussed				
	N	*M*	*SD*	*N*	*M*	*SD*	*p*	*t*
RT1	26	327.866	55.304	18	333.931	67.574	0.746	-0.327
CSL1	26	1207.597	234.592	18	1176.234	217.354	0.656	0.449
PRT1	26	619.007	108.165	18	612.132	147.672	0.859	0.178
SP1	26	1706.992	355.904	18	1490.531	300.871	0.041	2.109
GNG1	26	539.972	63.228	18	563.906	106.625	0.356	-0.934
CSD2	26	1074.090	187.137	18	1133.834	256.596	0.376	-0.894
MTS1	26	1667.365	261.038	18	1729.706	375.693	0.519	-0.650
MS1	26	910.263	220.549	18	797.416	202.616	0.092	1.724
RT2	26	345.570	39.562	18	337.914	45.576	0.556	0.593

There are significant differences mean reaction time on Spatial Processing between baselines for controls and 15 days after concussion for concussed athletes. No other differences are significant for the remaining DANA subtests for mean reaction time between baselines for controls and assessments 15 days after concussion for concussed athletes.

Baseline (controls) vs. 45 Day (concussed)								
	meanRT							
	Controls			Concussed				
	N	*M*	*SD*	*N*	*M*	*SD*	*p*	*t*
RT1	26	327.866	55.304	14	329.468	47.442	0.927	-0.092
CSL1	26	1207.597	234.592	14	1190.376	190.091	0.815	0.236
PRT1	26	619.007	108.165	14	600.013	102.247	0.593	0.540
SP1	26	1706.992	355.904	14	1500.196	270.644	0.066	1.895
GNG1	26	539.972	63.228	14	564.184	94.814	0.340	-0.967
CSD2	26	1074.090	187.137	14	1134.795	280.372	0.418	-0.820
MTS1	26	1667.365	261.038	14	1664.471	275.309	0.974	0.033
MS1	26	910.263	220.549	14	831.840	155.946	0.246	1.178
RT2	26	345.570	39.562	14	344.289	57.107	0.934	0.083

There are no significant differences in any of the DANA subtests for mean reaction time between baselines for controls and assessments 45 days after concussion for concussed athletes.

Baseline (controls) vs. 24-hour (concussed)								
	meanThru							
	Controls			Concussed				
	N	*M*	*SD*	*N*	*M*	*SD*	*p*	*t*
RT1	26	186.800	25.543	18	178.282	27.421	0.297	1.056
CSL1	26	49.216	9.242	18	47.924	8.563	0.641	0.470
PRT1	26	96.388	14.054	18	94.673	12.453	0.679	0.416
SP1	26	34.459	6.004	18	33.529	6.664	0.632	0.483
GNG1	26	105.607	24.883	18	106.890	17.029	0.850	-0.190
CSD2	26	53.694	8.714	18	52.811	10.568	0.764	0.303
MTS1	26	35.120	6.762	18	34.643	6.187	0.813	0.238
MS1	26	56.605	16.976	18	55.454	23.374	0.851	0.190
RT2	26	174.781	20.089	18	174.482	25.214	0.965	0.044

There are no significant differences in any of the DANA subtests for mean throughput between baselines for controls and 24-hour assessments of concussed athletes.

Baseline (controls) vs. 8 Day (concussed)								
	meanThru							
	Controls			Concussed				
	N	*M*	*SD*	*N*	*M*	*SD*	*p*	*t*
RT1	26	186.800	25.543	18	182.702	25.889	0.606	0.520
CSL1	26	49.216	9.242	18	50.606	10.593	0.647	-0.462
PRT1	26	96.388	14.054	18	96.192	13.411	0.963	0.046
SP1	26	34.459	6.004	18	35.436	5.953	0.597	-0.532
GNG1	26	105.607	24.883	18	110.632	17.945	0.467	-0.734
CSD2	26	53.694	8.714	18	51.790	13.548	0.573	0.568
MTS1	26	35.120	6.762	18	35.811	7.516	0.752	-0.318
MS1	26	56.605	16.976	18	61.062	20.279	0.434	-0.791
RT2	26	174.781	20.089	18	181.241	21.750	0.316	-1.014

There are no significant differences in any of the DANA subtests for mean throughput between baselines for controls and assessments 8 days after concussion for concussed athletes.

Baseline (controls) vs. 15 Day (concussed)								
	meanThru							
	Controls			Concussed				
	N	*M*	*SD*	*N*	*M*	*SD*	*p*	*t*
RT1	26	186.800	25.543	18	183.251	29.762	0.674	0.423
CSL1	26	49.216	9.242	18	50.801	9.945	0.591	-0.542
PRT1	26	96.388	14.054	18	99.989	18.103	0.462	-0.743
SP1	26	34.459	6.004	18	39.126	8.183	0.035	-2.184
GNG1	26	105.607	24.883	18	106.720	20.213	0.876	-0.157
CSD2	26	53.694	8.714	18	51.623	11.365	0.498	0.684
MTS1	26	35.120	6.762	18	33.022	7.547	0.340	0.965
MS1	26	56.605	16.976	18	66.251	21.373	0.103	-1.666
RT2	26	174.781	20.089	18	178.978	24.490	0.537	-0.623

There are significant differences mean throughput on Spatial Processing between baselines for controls and 15 days after concussion for concussed athletes. No other differences are significant for the remaining DANA subtests for mean throughput between baselines for controls and assessments 15 days after concussion for concussed athletes.

Baseline (controls) vs. 45 Day (concussed)								
	meanThru							
	Controls			Concussed				
	N	*M*	*SD*	*N*	*M*	*SD*	*p*	*t*
RT1	26	186.800	25.543	14	184.561	25.779	0.794	0.263
CSL1	26	49.216	9.242	14	49.871	8.017	0.824	-0.223
PRT1	26	96.388	14.054	14	99.753	13.793	0.472	-0.727
SP1	26	34.459	6.004	14	38.857	6.327	0.036	-2.169
GNG1	26	105.607	24.883	14	108.262	17.968	0.727	-0.352
CSD2	26	53.694	8.714	14	51.341	13.367	0.505	0.673
MTS1	26	35.120	6.762	14	34.589	6.895	0.815	0.235
MS1	26	56.605	16.976	14	64.505	23.139	0.225	-1.234
RT2	26	174.781	20.089	14	175.001	27.780	0.977	-0.029

There are significant differences mean throughput on Spatial Processing between baselines for controls and 45 days after concussion for concussed athletes. No other differences are significant for the remaining DANA subtests for mean throughput between baselines for controls and assessments 45 days after concussion for concussed athletes.

Baseline (controls) vs. 24-hour (concussed)								
	percentCorrect							
	Controls			Concussed				
	N	*M*	*SD*	*N*	*M*	*SD*	*p*	*t*
RT1	26	99.423	2.481	18	98.611	2.604	0.301	1.046
CSL1	26	95.299	3.493	18	95.602	3.993	0.791	-0.266
PRT1	26	96.755	3.901	18	97.049	2.507	0.780	-0.281
SP1	26	94.231	5.233	18	90.556	8.382	0.080	1.792
GNG1	26	94.872	19.487	18	99.445	1.278	0.328	-0.990
CSD2	26	92.628	5.876	18	91.512	4.994	0.515	0.657
MTS1	26	89.487	6.160	18	88.704	6.968	0.696	0.393
MS1	26	80.256	20.932	18	74.259	30.137	0.440	0.780
RT2	26	98.269	2.896	18	97.361	5.654	0.488	0.699

There are no significant differences in any of the DANA subtests for percent correct between baselines for controls and 24-hour assessments of concussed athletes.

Baseline (controls) vs. 8 Day (concussed)								
	percentCorrect							
	Controls			Concussed				
	N	*M*	*SD*	*N*	*M*	*SD*	*p*	*t*
RT1	26	99.423	2.481	18	99.306	1.673	0.862	0.175
CSL1	26	95.299	3.493	18	96.142	3.180	0.419	-0.816
PRT1	26	96.755	3.901	18	95.833	3.865	0.444	0.773
SP1	26	94.231	5.233	18	89.722	6.960	0.018	2.454
GNG1	26	94.872	19.487	18	98.704	1.672	0.412	-0.829
CSD2	26	92.628	5.876	18	89.969	9.293	0.251	1.164
MTS1	26	89.487	6.160	18	89.074	5.578	0.821	0.227
MS1	26	80.256	20.932	18	80.926	21.107	0.918	-0.104
RT2	26	98.269	2.896	18	99.167	1.485	0.234	-1.207

There are significant differences percent correct on Spatial Processing between baselines for controls and 8 days after concussion for concussed athletes. No other differences are significant for the remaining DANA subtests for percent correct between baselines for controls and assessments 8 days after concussion for concussed athletes.

Baseline (controls) vs. 15 Day (concussed)								
	percentCorrect							
	Controls			Concussed				
	N	*M*	*SD*	*N*	*M*	*SD*	*p*	*t*
RT1	26	99.423	2.481	18	97.500	4.926	0.095	1.708
CSL1	26	95.299	3.493	18	96.065	3.097	0.459	-0.748
PRT1	26	96.755	3.901	18	97.917	2.626	0.277	-1.101
SP1	26	94.231	5.233	18	92.500	4.926	0.276	1.104
GNG1	26	94.872	19.487	18	97.408	6.216	0.598	-0.532
CSD2	26	92.628	5.876	18	90.278	7.395	0.247	1.173
MTS1	26	89.487	6.160	18	86.667	5.717	0.132	1.537
MS1	26	80.256	20.932	18	86.667	23.066	0.344	-0.958
RT2	26	98.269	2.896	18	98.611	1.762	0.658	-0.446

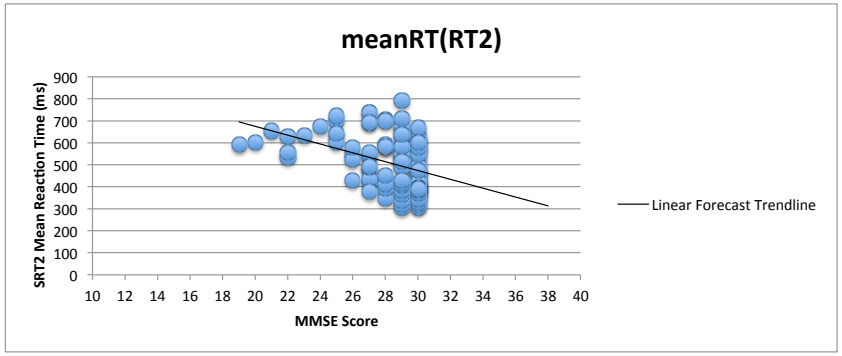
There are no significant differences in any of the DANA subtests for percent correct between baselines for controls and assessments 15 days after concussion for concussed athletes.

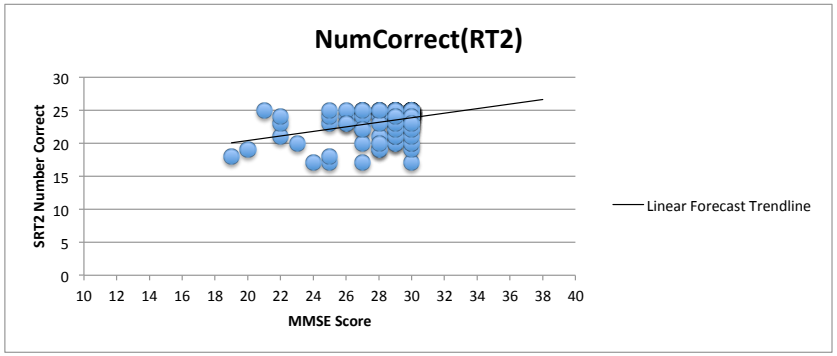
Baseline (controls) vs. 45 Day (concussed)								
	percentCorrect							
	Controls			Concussed				
	N	*M*	*SD*	*N*	*M*	*SD*	*p*	*t*
RT1	26	99.423	2.481	14	99.464	1.447	0.955	-0.057
CSL1	26	95.299	3.493	14	96.925	2.840	0.144	-1.493
PRT1	26	96.755	3.901	14	97.545	2.789	0.507	-0.669
SP1	26	94.231	5.233	14	93.929	5.942	0.869	0.166
GNG1	26	94.872	19.487	14	99.286	1.419	0.405	-0.841
CSD2	26	92.628	5.876	14	88.492	11.471	0.138	1.516
MTS1	26	89.487	6.160	14	90.000	7.845	0.821	-0.228
MS1	26	80.256	20.932	14	82.143	22.517	0.793	-0.265
RT2	26	98.269	2.896	14	97.857	2.373	0.651	0.456

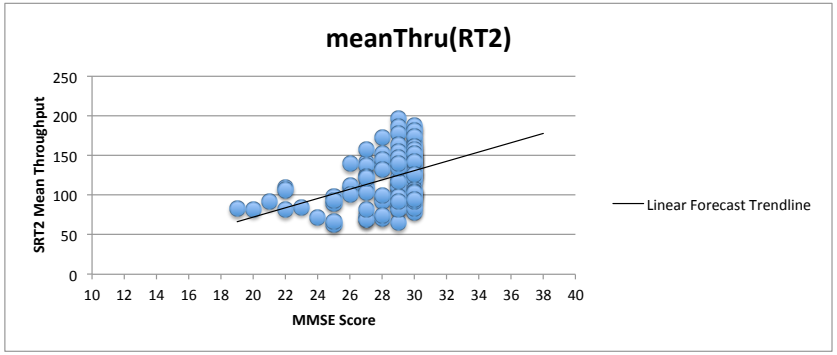
There are no significant differences in any of the DANA subtests for percent correct between baselines for controls and assessments 45 days after concussion for concussed athletes.

Appendix O: ECT Statistics: DANA vs. MMSE

patientName	MMSE Score	TestDate	meanRT(RT2)	NumCorrect(RT2)	meanThru(RT2)
1	26	1/13/14	545.2	24	108.59
1	25	1/14/14	639.28	23	89.522
1	20	1/23/14	604.04	19	82.428
1	25	1/27/14	699.6	17	62.441
1	22	1/28/14	630.08	21	81.673
1	19	2/3/14	590.68	18	82.997
1	23	2/4/14	633.84	20	84.611
1	22	2/10/14	535.48	23	109.57
1	22	2/11/14	556.08	24	106.32
2	29	1/22/14	306.2	25	195.95
2	29	1/28/14	322.84	25	185.85
2	28	2/18/14	348.24	25	172.29
2	30	2/24/14	350.84	25	171.02
2	29	3/5/14	336.4	25	178.36
3	25	2/4/14	602.76	24	97.565
3	27	2/10/14	423.92	25	141.54
3	30	2/11/14	479.68	25	125.08
3	30	2/17/14	641.32	17	78.524
3	29	2/18/14	537.2	22	108.26
3	29	3/10/14	581.72	20	95.589
3	27	3/21/14	479.12	24	124.79
3	30	3/24/14	467.6	24	128.12
3	29	3/25/14	420.64	25	142.64
3	27	3/31/14	436.16	25	137.56
3	30	4/1/14	627.56	19	84.206
3	28	4/9/14	584.32	21	96.148
3	28	4/14/14	591.56	19	92.278
3	29	4/15/14	559.44	20	101.2
3	29	4/21/14	503.68	23	117.64
3	27	4/22/14	689.68	17	69.07
3	27	5/5/14	536.92	23	109.23
3	26	6/19/14	525.32	23	112.03
3	29	7/2/14	629.52	22	89.093
3	28	7/9/14	408.4	24	137.2
3	29	7/23/14	559	21	102.01
5	28	2/11/14	432.88	25	138.61
5	30	2/18/14	413.88	25	144.97
5	30	2/24/14	435.64	24	138.36
5	30	2/25/14	507.12	25	118.32
6	30	2/6/14	414.52	23	148.27
6	30	2/10/14	355.56	25	168.75
6	29	2/11/14	367.44	25	163.29
10	30	3/20/14	403.12	24	150.62
10	30	3/25/14	423.08	25	141.82
10	30	3/31/14	385.04	25	155.83
10	30	4/1/14	405.08	25	148.12
10	29	4/9/14	388	25	154.64
10	30	4/10/14	437.4	25	137.17
10	30	4/15/14	419.96	25	142.87
10	30	4/22/14	365.72	25	164.06



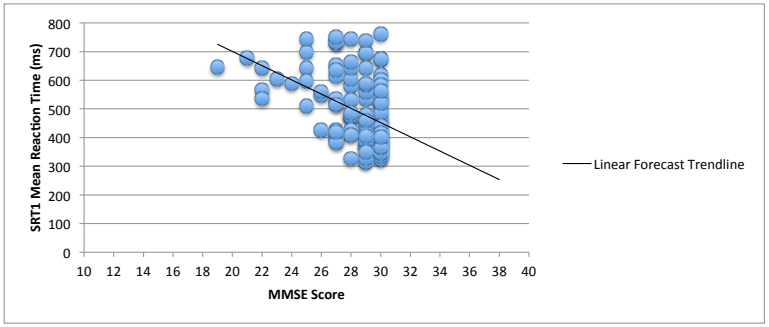


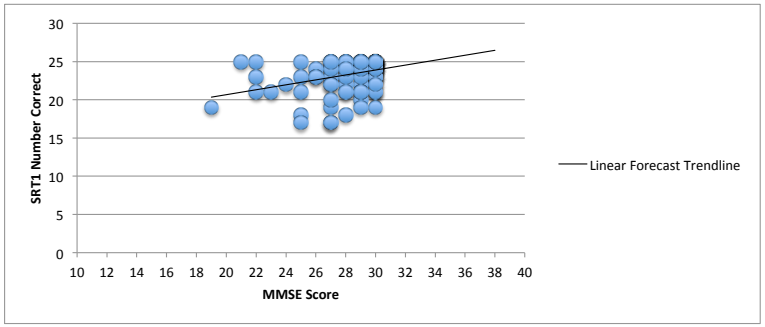


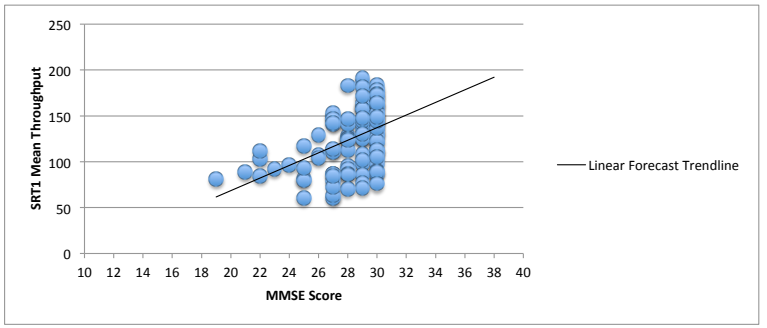
10	30	4/24/14	399.96	24	138.84
14	27	7/29/14	738.4	22	73.706
19	29	6/5/14	526.08	25	114.05
19	30	6/10/14	475.32	25	126.23
19	30	6/17/14	525.92	25	114.09
20	28	6/4/14	394.32	25	152.16
20	28	6/11/14	412.96	25	145.29
20	26	6/13/14	430.08	25	139.51
20	27	6/16/14	488.8	25	122.75
20	29	7/9/14	486.04	23	122.65
21	30	7/28/14	323.04	25	185.74
21	30	8/5/14	367.88	25	163.1
21	30	8/11/14	308.2	24	179.67
21	30	8/12/14	320.28	25	187.34
21	30	8/18/14	330.4	25	181.6
21	30	8/19/14	345.32	25	173.75
21	30	8/21/14	375.8	25	159.66
21	30	8/25/14	387.56	25	154.81
21	30	8/26/14	370.68	25	161.86
21	29	8/28/14	381.44	24	145.39
21	30	9/4/14	388.56	23	146.22
21	27	9/9/14	380.24	25	157.8
21	30	9/11/14	381.52	25	157.27
22	30	7/29/14	453.8	24	132.35
23	30	7/24/14	571.04	23	101.76
23	28	7/29/14	582.64	23	99.452
24	30	8/18/14	578	24	102.02
24	29	8/19/14	664.84	21	81.284
24	30	8/21/14	546.88	22	105.87
25	30	7/31/14	403.16	24	150.6
25	30	8/5/14	464.96	23	129.23
25	30	8/7/14	491.04	25	122.19
25	30	8/12/14	572.84	23	101.4
25	30	8/14/14	425.6	25	140.98
25	30	8/19/14	452.48	24	132.77
25	30	8/21/14	614.36	20	88.406
25	29	8/25/14	407.28	25	147.32
27	29	8/5/14	790.96	21	65.438
27	29	8/7/14	548.12	25	109.47
27	30	8/12/14	614.36	24	95.608
27	29	8/18/14	675.4	24	86.481
27	30	8/26/14	586.64	25	102.28
27	27	8/28/14	738.12	20	68.802
27	28	9/2/14	708.24	19	70.405
27	29	9/5/14	709.4	24	82.115
27	30	9/9/14	618.6	25	96.993
27	21	9/18/14	654.28	25	91.704
27	27	9/23/14	693.4	23	81.725
27	25	9/25/14	722.68	18	66.083
27	28	9/29/14	698.56	20	74.051
27	30	10/7/14	667.64	22	83.025

28	29	8/13/14	584.24	22	97.564
28	29	8/18/14	635.6	24	92.221
28	27	8/19/14	544.6	24	108.72
28	24	8/26/14	672.36	17	72.182
28	25	8/28/14	643.96	25	93.173
28	26	9/2/14	576.2	23	100.72
28	27	9/3/14	558.48	22	103.14
29	30	8/19/14	497.72	25	120.55
29	30	8/21/14	553.88	24	106.77
29	30	8/25/14	462.48	25	129.74
29	30	8/28/14	545.56	20	105.04
29	30	9/2/14	603.32	21	92.171
29	30	9/11/14	424.04	24	142.5
29	29	9/15/14	514	25	116.73
29	30	9/16/14	395.48	25	151.71
32	30	8/20/14	578.12	25	103.78
32	30	8/28/14	601.8	22	94.095
32	30	9/2/14	392.92	25	152.7
32	28	9/3/14	452.92	25	132.47
32	27	9/4/14	493.44	25	121.6
33	29	8/26/14	415.56	23	134.01
33	30	8/28/14	391.04	24	143.03
33	30	9/3/14	473.84	23	126.38
33	29	9/4/14	430.24	24	140.26

patientName	MMSE Score	TestDate	meanRT(RT1)	NumCorrect(RT1)	meanThru(RT1)
1	26	1/13/14	549.8	24	107.62
1	25	1/14/14	511.16	25	117.38
1	25	1/27/14	698.52	23	81.057
1	22	1/28/14	643.36	21	84.781
1	19	2/3/14	644.92	19	80.798
1	23	2/4/14	603.52	21	92.131
1	22	2/10/14	566.12	23	102.78
1	22	2/11/14	535.88	25	111.97
2	29	1/22/14	321.04	25	186.89
2	29	1/28/14	314.48	25	190.79
2	28	2/18/14	327.36	25	183.28
2	30	2/24/14	336.44	25	178.34
2	29	3/5/14	330.4	25	181.6
3	25	2/4/14	642.48	18	79.656
3	27	2/10/14	399.24	25	150.29
3	30	2/11/14	532.2	21	109.06
3	30	2/17/14	425.28	23	130.46
3	29	2/18/14	444	25	135.14
3	29	3/10/14	417.32	24	145.01
3	27	3/21/14	411.12	24	147.41
3	30	3/24/14	377.92	23	151.16
3	29	3/25/14	375.2	25	159.91
3	27	3/31/14	425.84	25	140.9
3	28	4/9/14	467.6	23	128.37
3	27	4/10/14	392.6	25	152.83
3	28	4/14/14	476	23	125.7
3	29	4/15/14	533.48	20	108.63
3	29	4/21/14	560	19	100.74
3	27	4/22/14	747.68	17	60.355
3	27	5/5/14	520.64	23	113.2
3	26	6/19/14	426.92	23	129.63
3	29	7/2/14	472.72	24	126.62
3	28	7/9/14	476.56	24	125.51
3	28	7/18/14	416.28	24	145.41
3	29	7/23/14	366.12	25	163.88
5	28	2/11/14	427.04	25	140.5
5	30	2/18/14	347.92	25	172.45
5	30	2/24/14	335.84	25	178.66
5	30	2/25/14	493.32	23	120.54
6	30	2/6/14	417.96	22	149.9
6	30	2/10/14	377.68	25	158.86
6	29	2/11/14	381.12	25	157.43
10	30	3/20/14	355.72	25	168.67
10	30	3/25/14	395.64	25	151.65
10	30	3/31/14	351.16	25	170.86
10	30	4/1/14	387.48	25	154.85
10	29	4/9/14	387.36	24	157.38
10	30	4/10/14	461.88	25	129.9
10	30	4/15/14	400.2	25	149.93
10	30	4/22/14	372.52	25	161.07
10	30	4/24/14	416.84	25	143.94
14	27	7/29/14	652.68	23	87.456
19	29	6/5/14	476	25	126.05
19	30	6/10/14	447.76	25	134
19	30	6/17/14	556.56	19	101.76



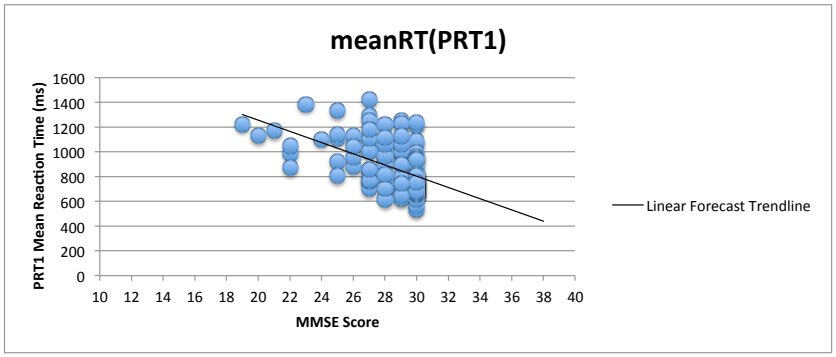


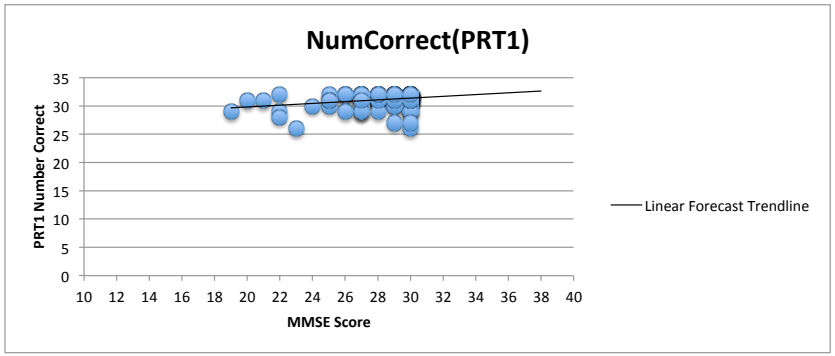


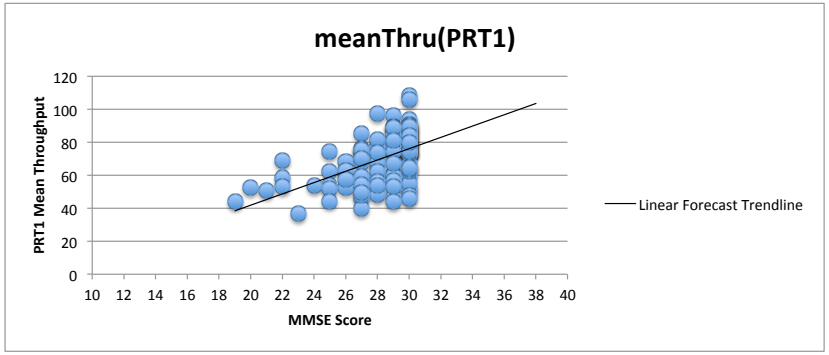
20	28	6/4/14	409.04	25	146.68
20	28	6/11/14	579.8	18	94.887
20	27	6/16/14	536.44	24	110.49
20	29	7/9/14	582.8	22	97.86
21	30	7/28/14	326.32	25	183.87
21	30	8/5/14	335.52	25	178.83
21	30	8/11/14	356.52	25	168.29
21	30	8/12/14	380.12	24	160.69
21	30	8/18/14	344.88	25	173.97
21	30	8/19/14	345.96	25	173.43
21	30	8/21/14	376.92	24	162.2
21	30	8/25/14	367.36	23	153.33
21	30	8/26/14	457.08	24	131.32
21	29	8/28/14	426.72	24	141.52
21	30	9/4/14	374.92	24	163.15
21	27	9/9/14	382.48	23	146.47
21	30	9/11/14	407.16	23	136.53
22	30	7/29/14	390.68	24	142.24
23	27	7/9/14	728.36	17	63.003
23	30	7/24/14	522.28	22	112.16
23	28	7/29/14	604.04	21	92.027
24	30	8/18/14	618	21	89.316
24	29	8/19/14	642.6	21	84.91
24	30	8/21/14	602.6	24	97.593
25	30	7/31/14	367.84	25	163.11
25	30	8/5/14	456.76	24	131.42
25	30	8/7/14	412.08	25	145.6
25	30	8/12/14	423.52	24	142.69
25	30	8/14/14	416.52	24	145.32
25	30	8/19/14	584.28	21	89.68
25	30	8/21/14	455.04	23	121.55
25	29	8/25/14	416.36	25	144.11
27	29	8/5/14	696.72	25	86.118
27	29	8/7/14	588.96	25	101.87
27	30	8/12/14	532.28	25	112.72
27	29	8/18/14	694.92	21	76.846
27	28	8/19/14	533	25	112.57
27	28	8/22/14	643.24	22	86.81
27	30	8/26/14	675.52	24	86.465
27	27	8/28/14	733.8	24	79.243
27	28	9/2/14	662.08	23	86.063
27	29	9/5/14	738.68	21	71.191
27	30	9/9/14	674.84	25	88.91
27	21	9/18/14	677.44	25	88.569
27	27	9/23/14	749.36	22	72.446
27	25	9/25/14	743.96	17	60.847
27	28	9/29/14	744.08	21	70.551
27	30	10/7/14	761.56	24	76.211
28	29	8/13/14	478.64	23	124.89
28	27	8/19/14	613.52	19	87.181
28	27	8/21/14	635.76	20	84.255
28	24	8/26/14	589.56	22	96.486
28	25	8/28/14	596.36	21	93.589
28	26	9/2/14	560.8	23	103.9
28	27	9/3/14	514.96	22	114.17
29	30	8/19/14	534.6	25	112.23

29	30	8/21/14	543.2	24	109.02
29	30	8/25/14	472.88	25	126.88
29	30	8/28/14	485.76	23	122.74
29	30	9/2/14	520.88	22	112.54
29	30	9/11/14	391.04	25	153.44
29	29	9/15/14	459.96	24	130.43
29	30	9/16/14	428.92	24	140.73
32	30	8/20/14	561.72	24	105.18
32	30	8/28/14	440.36	24	136.75
32	30	9/2/14	415.4	25	144.44
32	28	9/3/14	483.96	24	123.44
32	27	9/4/14	420.52	25	142.68
33	29	8/26/14	350.04	25	171.41
33	30	8/28/14	365.76	25	164.04
33	30	9/3/14	402.48	25	149.08
33	29	9/4/14	405.52	25	147.96
Mininum			314.48		
Maximum			761.56		

patientName	MMSE Score	TestDate	meanRT(PRT1)	NumCorrect(PRT1)	meanThru(PRT1)
1	26	1/13/14	881.44	32	68.071
1	25	1/14/14	922.03	30	62.576
1	20	1/23/14	1135.5	31	52.478
1	25	1/27/14	1113.6	31	53.573
1	22	1/28/14	984.81	29	58.286
1	19	2/3/14	1223.4	29	44.236
1	23	2/4/14	1386.7	26	36.696
1	22	2/10/14	1046.9	28	52.973
1	22	2/11/14	870.75	32	68.906
2	29	1/22/14	742.38	30	80.231
2	29	1/28/14	622.38	32	96.405
2	28	2/18/14	616.97	32	97.25
2	30	2/24/14	678.06	32	88.487
2	29	3/5/14	682.31	32	87.936
3	25	2/4/14	808.44	32	74.217
3	27	2/10/14	775.94	31	74.182
3	30	2/11/14	652.94	29	82.421
3	30	2/17/14	731.78	31	78.438
3	29	2/18/14	721.69	32	83.138
3	29	3/10/14	717.06	31	81.063
3	27	3/21/14	702.53	32	85.405
3	30	3/24/14	671.66	31	85.885
3	29	3/25/14	727.66	32	82.457
3	27	3/31/14	808.66	32	74.197
3	30	4/1/14	1070.8	29	51.157
3	28	4/9/14	823.06	31	70.361
3	27	4/10/14	860.59	30	67.899
3	28	4/14/14	737.78	31	78.38
3	29	4/15/14	786	31	74.76
3	29	4/21/14	1026.9	31	58.389
3	27	4/22/14	757.53	30	76.406
3	27	5/5/14	1029.8	29	52.598
3	26	6/19/14	1127.1	29	52.444
3	29	7/2/14	781.75	31	75.588
3	28	7/9/14	930.81	31	63.321
3	28	7/18/14	781.19	32	76.806
3	29	7/23/14	997.72	32	60.137
5	28	2/11/14	702	31	81.848
5	30	2/18/14	735.91	32	81.532
5	30	2/24/14	685.62	32	87.511
5	30	2/25/14	740.91	32	80.982
6	30	2/6/14	830.41	31	73.327
6	30	2/10/14	833.22	31	73.06
6	29	2/11/14	747.22	31	76.905
10	30	3/20/14	666.25	32	90.056
10	30	3/25/14	693.66	32	86.498
10	30	3/31/14	732.75	32	81.883
10	30	4/1/14	696.66	32	86.126
10	29	4/9/14	671.5	32	89.352
10	30	4/10/14	773.34	32	77.585



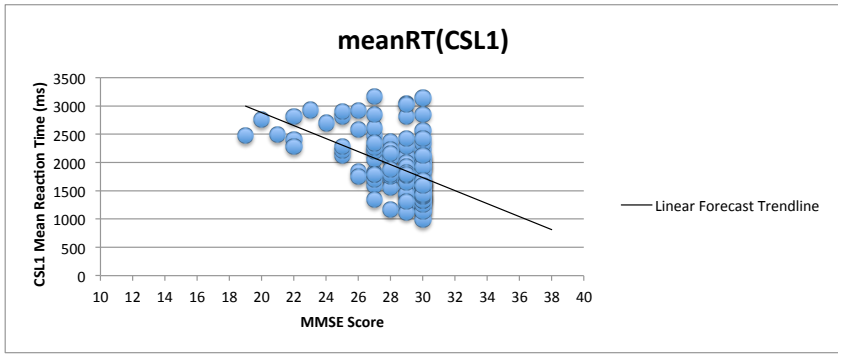


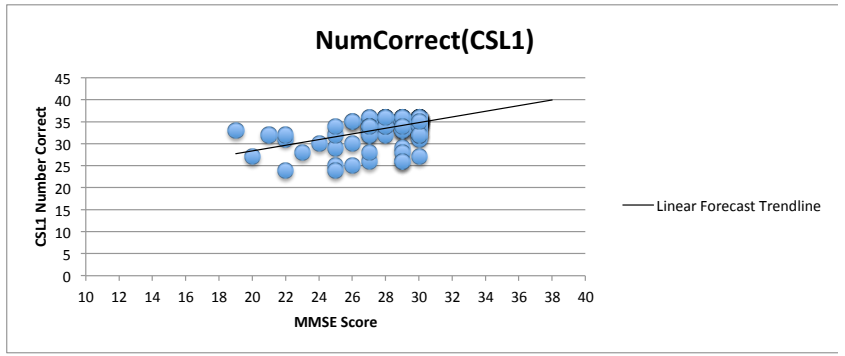


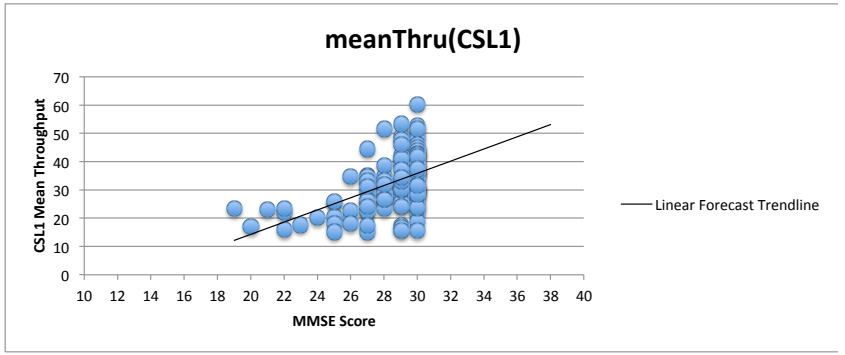
10	30	4/15/14	769.69	31	74.779
10	30	4/22/14	760.19	32	78.928
10	30	4/24/14	769.16	32	78.008
14	27	7/29/14	1296.7	32	46.271
19	29	6/5/14	803.25	32	74.697
19	30	6/10/14	759.47	32	79.003
19	30	6/17/14	950.22	30	59.113
20	28	6/4/14	888.31	32	67.544
20	28	6/11/14	1006.6	31	59.645
20	26	6/13/14	957.69	32	62.651
20	27	6/16/14	1116.6	32	53.735
20	29	7/9/14	990.91	32	60.551
21	30	7/28/14	535.09	31	108.04
21	30	8/5/14	565.28	32	106.14
21	30	8/11/14	653.5	32	91.813
21	30	8/12/14	615.84	31	93.672
21	30	8/18/14	700.5	32	85.653
21	30	8/19/14	808.22	32	74.237
21	30	8/21/14	744.91	30	73.417
21	30	8/25/14	712.09	32	84.259
21	30	8/26/14	757.47	32	79.211
21	29	8/28/14	708.53	32	84.682
21	30	9/4/14	738.31	32	81.266
21	27	9/9/14	770.56	31	75.361
21	30	9/11/14	805.31	32	74.505
22	30	7/29/14	661.66	32	90.682
23	27	7/9/14	1424.4	29	39.838
23	30	7/24/14	1089.2	29	51.591
23	28	7/29/14	1098.3	29	50.617
24	30	8/18/14	893.25	31	65.222
24	29	8/19/14	1256.3	30	46.615
24	30	8/21/14	998.69	26	55.054
25	30	7/31/14	654.88	31	88.275
25	30	8/5/14	658.62	31	88.916
25	30	8/7/14	694.72	32	86.366
25	30	8/12/14	712.59	32	84.199
25	30	8/14/14	859.03	31	67.179
25	30	8/19/14	819.41	32	73.224
25	30	8/21/14	737.41	31	77.922
25	29	8/25/14	675.06	32	88.881
27	29	8/5/14	1041.5	32	57.609
27	29	8/7/14	1000.2	32	59.985
27	30	8/12/14	959.25	32	62.549
27	29	8/18/14	1085.8	31	55.029
27	28	8/19/14	966.62	32	62.072
27	28	8/22/14	1226	31	48.395
27	30	8/26/14	1215.6	29	47.931
27	27	8/28/14	1061.4	31	54.385
27	28	9/2/14	1060.7	32	56.569
27	29	9/5/14	1059	32	56.656
27	30	9/9/14	945.03	32	63.49

27	21	9/18/14	1175.4	31	50.596
27	27	9/23/14	1008.5	32	59.494
27	25	9/25/14	1144.5	31	52.043
27	28	9/29/14	1115.5	32	53.786
27	30	10/7/14	1239.6	27	46.072
28	29	8/13/14	1230.7	27	43.855
28	29	8/18/14	1127.9	32	53.196
28	27	8/19/14	1256.9	32	47.735
28	27	8/21/14	1109.5	32	54.08
28	24	8/26/14	1102.8	30	53.933
28	25	8/28/14	1332.6	31	44.335
28	26	9/2/14	1041.4	32	57.616
28	27	9/3/14	1177.6	29	49.769
29	30	8/19/14	803.16	32	74.705
29	30	8/21/14	773.91	32	77.529
29	30	8/25/14	666.69	32	89.997
29	30	8/28/14	734.91	32	81.643
29	30	9/2/14	721.81	31	79.842
29	30	9/11/14	824.28	32	72.791
29	29	9/15/14	897.19	32	66.876
29	30	9/16/14	670.16	32	89.531
32	30	8/20/14	787.72	31	73.899
32	30	8/28/14	936.19	31	64.449
32	30	9/2/14	807.75	32	74.28
32	28	9/3/14	813.62	32	73.744
32	27	9/4/14	862.41	31	70.394
33	29	8/26/14	648.34	31	88.854
33	30	8/28/14	683.5	31	84.204
33	30	9/3/14	751.19	32	79.874
33	29	9/4/14	742.66	32	80.791

patientName	MMSE Score	TestDate	meanRT(CSL1)	NumCorrect(CSL1)	meanThru(CSL1)
1	26	1/13/14	1846.8	24.99984	20.008
1	25	1/14/14	2130.1	24.99984	20.631
1	20	1/23/14	2759.5	27	16.987
1	25	1/27/14	2806.3	29.00016	18.188
1	22	1/28/14	2406.6	30.99996	21.903
1	19	2/3/14	2480.9	33.00012	23.276
1	23	2/4/14	2928.8	28.00008	17.534
1	22	2/10/14	2817.7	24.00012	16.009
1	22	2/11/14	2283.7	32.00004	23.586
2	29	1/22/14	1415.7	34.99992	40.949
2	29	1/28/14	1227.5	36	48.881
2	28	2/18/14	1165.8	36	51.467
2	30	2/24/14	1292.8	33.99984	43.728
2	29	3/5/14	1258.6	36	47.671
3	25	2/4/14	2219	32.00004	25.629
3	27	2/10/14	1594.6	33.99984	35.002
3	30	2/11/14	1599.3	33.99984	36.623
3	30	2/17/14	1830.8	32.00004	29.735
3	29	2/18/14	2220.8	29.00016	24.796
3	29	3/10/14	1555.6	34.99992	39.261
3	27	3/21/14	1349.7	36	44.455
3	30	3/24/14	1434.2	36	41.836
3	29	3/25/14	1428.1	36	42.014
3	27	3/31/14	1831.3	33.00012	32.86
3	30	4/1/14	2072.6	33.00012	27.492
3	28	4/9/14	1844.4	34.99992	32.719
3	27	4/10/14	2044.6	34.99992	29.332
3	28	4/14/14	2100.3	36	28.567
3	29	4/15/14	1457.6	36	41.162
3	29	4/21/14	2115.9	36	28.357
3	27	4/22/14	1696.8	34.99992	34.748
3	27	5/5/14	2223.8	33.00012	25.989
3	26	6/19/14	1748	34.99992	34.646
3	29	7/2/14	1739.3	33.00012	31.958
3	28	7/9/14	1719.8	36	34.888
3	28	7/18/14	1557.1	36	38.532
3	29	7/23/14	1731.9	33.00012	31.808
5	28	2/11/14	1762.9	33.99984	32.254
5	30	2/18/14	1586.7	36	37.814
5	30	2/24/14	1460.1	36	41.094
5	30	2/25/14	1504.6	34.99992	39.24
6	30	2/6/14	2099.1	34.99992	28.527
6	30	2/10/14	1924.1	36	31.184
6	29	2/11/14	1719.3	34.99992	33.708
10	30	3/20/14	1150.2	36	52.165
10	30	3/25/14	1138.9	36	52.683
10	30	3/31/14	1221.8	36	49.108
10	30	4/1/14	1247.1	36	48.11
10	29	4/9/14	1126.1	36	53.281
10	30	4/10/14	1340.4	36	44.761



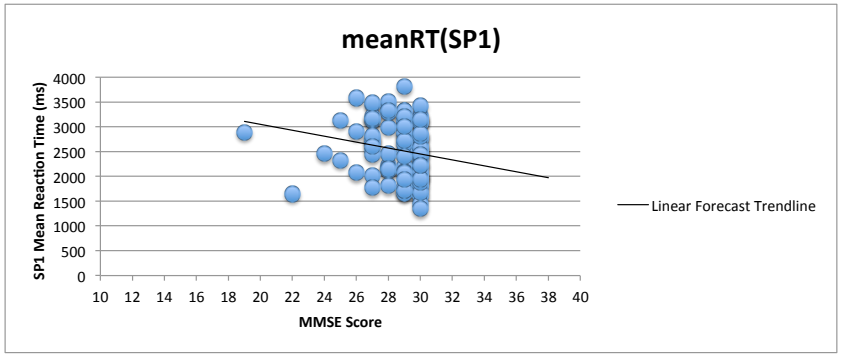


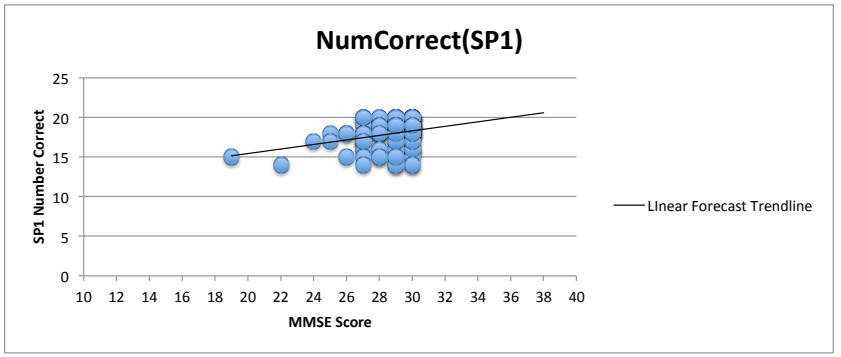


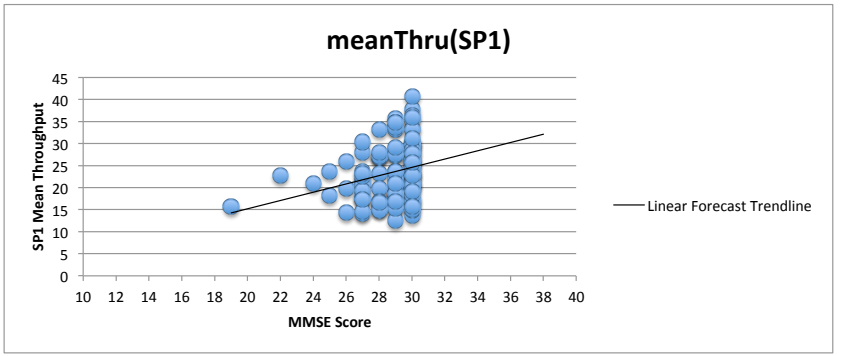
10	30	4/15/14	1506.1	34.99992	39.097
10	30	4/22/14	1347	36	44.543
10	30	4/24/14	1383.3	34.99992	42.282
14	27	7/29/14	2477.3	32.00004	22.381
19	29	6/5/14	2041.7	34.99992	28.612
19	30	6/10/14	2021	36	29.688
19	30	6/17/14	2566.7	33.00012	21.837
20	28	6/4/14	2130.9	36	28.157
20	28	6/11/14	2172.9	36	27.613
20	26	6/13/14	2591.7	34.99992	22.863
20	27	6/16/14	2201.8	34.99992	26.302
20	29	7/9/14	2112.4	34.99992	27.564
21	30	7/28/14	994.67	36	60.322
21	30	8/5/14	1139.9	34.99992	51.525
21	30	8/11/14	1260.6	34.99992	46.161
21	30	8/12/14	1652.5	36	36.308
21	30	8/18/14	1595.9	34.99992	38.196
21	30	8/19/14	1721.2	34.99992	33.635
21	30	8/21/14	1403.6	36	42.748
21	30	8/25/14	1359.6	34.99992	43.277
21	30	8/26/14	1328.2	36	45.174
21	29	8/28/14	1638	34.99992	37.143
21	30	9/4/14	1679.1	36	35.734
21	27	9/9/14	1791.9	36	33.484
21	30	9/11/14	1619.4	34.99992	37.602
22	30	7/29/14	1512.6	36	39.666
23	27	7/9/14	2608.7	33.99984	22.426
23	30	7/24/14	2121.9	32.00004	25
23	28	7/29/14	2365.8	32.00004	23.457
24	30	8/18/14	2855.8	30.99996	18.764
24	29	8/19/14	2817.8	25.99992	17.363
24	30	8/21/14	3138.7	27	15.673
25	30	7/31/14	1325.7	34.99992	44.018
25	30	8/5/14	1397.7	36	42.928
25	30	8/7/14	1651.5	36	36.331
25	30	8/12/14	1710.2	34.99992	33.867
25	30	8/14/14	2225.5	32.00004	25.356
25	30	8/19/14	1660.8	33.99984	34.133
25	30	8/21/14	2343.9	32.00004	23.618
25	29	8/25/14	1775.7	34.99992	33.07
27	29	8/5/14	2276.9	33.99984	25.777
27	29	8/7/14	2421.2	33.00012	24.148
27	30	8/12/14	1952.4	34.99992	30.272
27	29	8/18/14	2007.6	36	29.886
27	28	8/19/14	1795.1	36	33.425
27	28	8/22/14	2073.1	36	28.942
27	30	8/26/14	1911.7	36	31.386
27	27	8/28/14	2271.4	33.99984	26.118
27	28	9/2/14	2239.5	33.99984	26.53
27	29	9/5/14	1927.2	34.99992	30.297
27	30	9/9/14	1604.1	36	37.404

27	21	9/18/14	2486.2	32.00004	23.219
27	27	9/23/14	2346.1	32.00004	24.258
27	25	9/25/14	2284.9	33.99984	25.946
27	28	9/29/14	2165.6	33.99984	26.603
27	30	10/7/14	2077.1	33.99984	27.958
28	29	8/13/14	3047.3	28.00008	16.645
28	29	8/18/14	3032.9	25.99992	15.728
28	27	8/21/14	3170.1	25.99992	15.101
28	24	8/26/14	2700.4	29.99988	20.159
28	25	8/28/14	2896.1	24.00012	15.158
28	26	9/2/14	2914.8	29.99988	18.183
28	27	9/3/14	2847.8	28.00008	17.421
29	30	8/19/14	1850	33.99984	31.061
29	30	8/21/14	1977.2	36	30.346
29	30	8/25/14	1984.7	33.00012	29.58
29	30	8/28/14	1603.3	34.99992	36.258
29	30	9/2/14	1926.3	34.99992	31.244
29	30	9/11/14	1451.4	33.99984	39.506
29	29	9/15/14	1815.9	36	33.041
29	30	9/16/14	1413.8	36	42.439
32	30	8/20/14	2419.4	33.99984	23.779
32	30	8/28/14	2123.9	36	28.25
32	30	9/2/14	1679.8	32.00004	31.548
32	28	9/3/14	1881.7	36	31.886
32	27	9/4/14	1794.7	33.99984	31.279
33	29	8/26/14	1304.4	36	46
33	30	8/28/14	1438	36	41.724
33	30	9/3/14	1595.9	34.99992	37.359
33	29	9/4/14	1779.1	33.99984	34.375

patientName	MMSE Score	TestDate	meanRT(SP1)	NumCorrect(SP1)	meanThru(SP1)
1	19	2/3/14	2890.2	15	15.657
1	22	2/11/14	1648.5	14	22.766
2	29	1/22/14	1681.2	20	35.688
2	29	1/28/14	1659	19	34.759
2	28	2/18/14	1809.2	20	33.163
2	30	2/24/14	2019.2	20	29.715
2	29	3/5/14	3135.2	19	18.644
3	25	2/4/14	2328.3	18	23.661
3	27	2/10/14	2008	19	27.949
3	30	2/11/14	1604.4	15	25.983
3	30	2/17/14	2230.2	19	25.541
3	29	2/18/14	2496.6	19	23.657
3	29	3/10/14	1718.5	19	33.343
3	27	3/21/14	1767.3	17	30.395
3	30	3/24/14	1593.5	20	37.652
3	29	3/25/14	2201.8	20	27.25
3	27	3/31/14	2792.8	20	21.484
3	30	4/1/14	2608.6	19	22.959
3	28	4/9/14	2166.2	18	26.78
3	27	4/10/14	2707.4	16	20.789
3	28	4/14/14	2225.2	19	27.415
3	29	4/15/14	3321	16	15.699
3	29	4/21/14	2860.4	16	18.958
3	27	4/22/14	2672.7	17	21.137
3	27	5/5/14	3128.2	16	17.663
3	26	6/19/14	3578.4	15	14.41
3	29	7/2/14	3114.3	17	17.451
3	28	7/9/14	2174.8	18	27.127
3	28	7/18/14	2123.6	19	27.101
3	29	7/23/14	2867.2	16	18.193
5	28	2/11/14	2453	18	23.188
5	30	2/18/14	3091.6	14	13.756
5	30	2/24/14	2402.4	16	20.313
6	30	2/6/14	3128.4	17	17.381
6	30	2/10/14	3228.5	16	14.966
6	29	2/11/14	2883.2	19	20.564
10	30	3/20/14	1801.5	20	33.307
10	30	3/25/14	1699.2	20	35.312
10	30	3/31/14	1984	20	30.243
10	30	4/1/14	1975.8	20	30.368
10	29	4/9/14	1781.3	20	33.682
10	30	4/10/14	2476.9	19	23.772
10	30	4/15/14	2318.3	20	25.88
10	30	4/22/14	2621.5	18	22.908
10	30	4/24/14	1966.8	19	29.398
14	27	7/29/14	2531.4	20	23.702
19	29	6/5/14	3031.6	17	16.866
19	30	6/10/14	2742.4	16	19.628
19	30	6/17/14	2559.6	17	20.753
20	28	6/4/14	2147.8	20	27.936



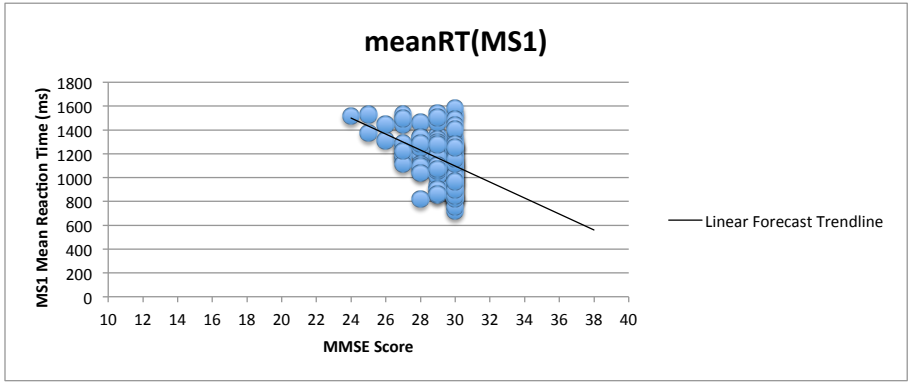


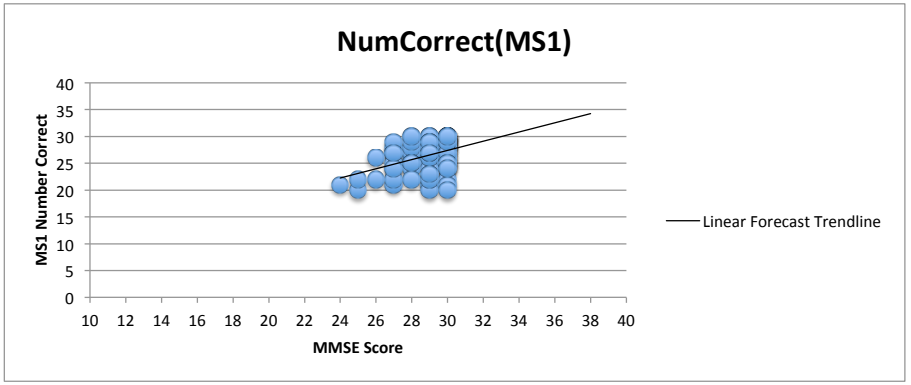


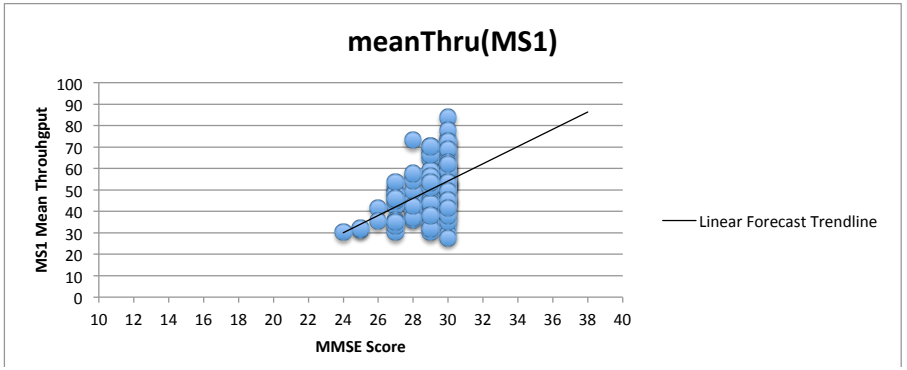
20	28	6/11/14	2994.6	19	19.73
20	26	6/13/14	2902.8	18	19.798
20	27	6/16/14	2744.4	18	20.651
20	29	7/9/14	2688.8	19	22.204
21	30	7/28/14	1445.2	18	36.462
21	30	8/5/14	1816.5	18	29.663
21	30	8/11/14	2054.6	18	26.623
21	30	8/12/14	2010.2	20	29.849
21	30	8/18/14	2607.8	19	22.966
21	30	8/19/14	2262.8	19	25.961
21	30	8/21/14	2439	19	24.737
21	30	8/25/14	2770.1	19	21.488
21	30	8/26/14	2531.4	18	23.924
21	29	8/28/14	2094.4	20	28.647
21	30	9/4/14	2828.7	18	20.87
21	27	9/9/14	3151.2	18	18.331
21	30	9/11/14	2152.7	20	27.873
22	30	7/29/14	2012.2	20	29.819
23	27	7/9/14	3445.5	15	14.059
23	30	7/24/14	3184.8	16	16.645
23	28	7/29/14	3406.1	15	15.308
24	29	8/19/14	3807.8	14	12.552
24	30	8/21/14	3194	16	16.872
25	30	7/31/14	1341.8	18	40.719
25	30	8/5/14	1810.1	20	33.147
25	30	8/7/14	1910.5	18	27.73
25	30	8/12/14	1987.2	19	28.2
25	30	8/14/14	1673.3	20	35.857
25	30	8/19/14	2094.8	20	28.642
25	30	8/21/14	1878	19	31.045
25	29	8/25/14	1721.7	20	34.85
27	29	8/5/14	3320.9	14	15.304
27	29	8/7/14	3132.5	19	18.786
27	30	8/12/14	3421.1	15	15.011
27	29	8/18/14	3209.7	20	18.693
27	28	8/19/14	3331.6	19	16.906
27	28	8/22/14	3506.4	16	15.321
27	30	8/26/14	2495.7	19	22.646
27	27	8/28/14	3208.1	17	17.636
27	28	9/2/14	3283.4	15	14.909
27	29	9/5/14	2653.6	17	18.712
27	30	9/9/14	2421.7	16	21.245
27	27	9/23/14	3484.8	14	14.635
27	30	10/7/14	3073.6	17	17.118
28	29	8/13/14	2402.8	18	23.613
28	29	8/18/14	2090.3	19	27.447
28	27	8/19/14	2816.8	18	19.362
28	27	8/21/14	2444.2	18	22.607
28	24	8/26/14	2460.8	17	20.996
28	25	8/28/14	3131.8	17	18.2
28	26	9/2/14	2070.6	18	25.991

28	27	9/3/14	2597.3	20	23.1
29	30	8/19/14	2587.6	18	22.719
29	30	8/21/14	2234.4	19	26.472
29	30	8/25/14	2828.4	18	20.151
29	30	8/28/14	1945.8	18	27.629
29	30	9/2/14	2439.1	20	24.599
29	30	9/11/14	2798.6	19	20.823
29	29	9/15/14	2728	19	21.078
29	30	9/16/14	2221.8	17	22.822
32	30	8/28/14	3120.8	18	18.298
32	30	9/2/14	2858.3	18	19.044
32	28	9/3/14	3326.5	18	16.722
32	27	9/4/14	3166.9	17	17.265
33	29	8/26/14	1935.8	19	29.172
33	30	8/28/14	2219.2	19	25.701
33	30	9/3/14	3141.2	14	15.805
33	29	9/4/14	3001.3	15	16.967

patientName	MMSE Score	TestDate	meanRT(MS1	NumCorrect(	meanThru(MS1)
2	29	1/22/14	902.23	27.9999	67.976
2	29	1/28/14	852.3	30	70.398
2	28	2/18/14	818.7	30	73.287
2	30	2/24/14	832	30	72.115
2	29	3/5/14	934.87	29.0001	64.578
3	25	2/4/14	1374.2	20.0001	31.502
3	27	2/10/14	1535.2	21.9999	30.332
3	30	2/11/14	1264.6	21	35.529
3	30	2/17/14	1345.4	24	39.319
3	29	2/18/14	1329.4	24.9999	39.7
3	29	3/10/14	1097.7	29.0001	54.377
3	27	3/21/14	1151.2	27.9999	50.776
3	30	3/24/14	1045.5	27	53.717
3	29	3/25/14	1229.1	27.9999	46.377
3	27	3/31/14	1194.2	27	48.882
3	30	4/1/14	1180.4	24.9999	44.753
3	28	4/9/14	1341.6	27.9999	43.256
3	27	4/10/14	1282.4	24	42.353
3	28	4/14/14	1190.3	26.0001	47.644
3	29	4/15/14	1220.1	24	44.785
3	29	4/21/14	1317.3	21	34.805
3	27	4/22/14	1477.2	24.9999	35.808
3	27	5/5/14	1256.7	27	44.943
3	29	7/2/14	1256.6	26.0001	44.434
3	28	7/9/14	1247.9	27	45.605
3	28	7/18/14	1058.5	27	56.613
3	29	7/23/14	1354.8	21	35.086
5	28	2/11/14	1107.5	27.9999	49.612
5	30	2/18/14	1130.1	27	52.252
5	30	2/24/14	863.77	30	69.463
5	30	2/25/14	1029.9	24.9999	51.839
6	30	2/6/14	1122.7	27.9999	52.828
6	30	2/10/14	1318.4	26.0001	42.76
6	29	2/11/14	1015.2	30	59.1
10	30	3/20/14	957.23	24.9999	54.681
10	30	3/25/14	963.77	30	62.256
10	30	3/31/14	904.67	29.0001	66.905
10	30	4/1/14	1198.2	26.0001	47.696
10	29	4/9/14	904.7	30	66.32
10	30	4/10/14	1062.4	30	56.474
10	30	4/15/14	1265.4	24.9999	43.069
10	30	4/22/14	1085.8	29.0001	55.014
10	30	4/24/14	1093.8	29.0001	54.586
14	27	7/29/14	1183.8	27	48.125
19	29	6/5/14	1081.6	29.0001	55.24
19	30	6/10/14	973.23	30	61.65







20	28	6/4/14	1314.3	24.9999	41.024
20	28	6/11/14	1096.2	29.0001	54.458
20	26	6/13/14	1310.7	26.0001	41.541
20	27	6/16/14	1291	21	35.074
20	29	7/9/14	1164	26.0001	45.125
21	30	7/28/14	716.87	30	83.698
21	30	8/5/14	856.43	27.9999	65.849
21	30	8/11/14	826.13	30	72.628
21	30	8/12/14	810.87	30	73.995
21	30	8/18/14	755	29.0001	77.662
21	30	8/19/14	832.17	30	72.101
21	30	8/21/14	1030.2	29.0001	58.191
21	30	8/25/14	825.73	30	72.663
21	30	8/26/14	890.97	30	67.343
21	29	8/28/14	865.9	29.0001	70.151
21	30	9/4/14	927.77	27.9999	64.421
21	27	9/9/14	1112.1	29.0001	53.63
21	30	9/11/14	1131.8	27.9999	52.349
22	30	7/29/14	947.33	29.0001	60.576
23	30	7/24/14	1527.4	21.9999	32.459
23	28	7/29/14	1460.5	24	36.21
24	30	8/18/14	1532.7	21	29.372
24	29	8/19/14	1541.8	20.0001	30.308
24	30	8/21/14	1584.6	20.0001	27.556
25	30	7/31/14	843.53	29.0001	68.763
25	30	8/5/14	1011.3	30	59.328
25	30	8/7/14	1104	27.9999	53.844
25	30	8/12/14	981.8	29.0001	61.266
25	30	8/14/14	899.8	27.9999	62.851
25	30	8/19/14	1177	27.9999	50.08
25	30	8/21/14	1251.8	26.0001	45.745
25	29	8/25/14	1056.7	27	56.088
27	29	8/5/14	1460.5	21.9999	33.986
27	29	8/7/14	1318.1	27.9999	43.25
27	30	8/12/14	1490.2	24	35.222
27	29	8/18/14	1302.4	27	42.987
27	28	8/22/14	1300.8	24.9999	40.128
27	30	8/26/14	1094	27.9999	54.034
27	27	8/28/14	1446.5	21.9999	33.121
27	28	9/2/14	1335.1	21.9999	37.136
27	29	9/5/14	1175.4	23.0001	43.915
27	30	9/9/14	1026.6	29.0001	58.405
27	27	9/23/14	1494.6	24	35.082
27	25	9/25/14	1526.9	21.9999	31.874
27	28	9/29/14	1287.8	24.9999	42.393
27	30	10/7/14	1440.2	26.0001	38.403
28	29	8/18/14	1502.7	21.9999	32.015

28	24	8/26/14	1516.6	21	30.454
28	26	9/2/14	1443.7	21.9999	35.442
29	30	8/19/14	1226.7	27	47.338
29	30	8/21/14	1300.6	24.9999	41.803
29	30	8/25/14	1260.6	26.0001	45.34
29	30	8/28/14	1019	30	58.881
29	30	9/2/14	1171.5	29.0001	50.748
29	30	9/11/14	1116.3	29.0001	53.414
29	29	9/15/14	1100.1	29.0001	50.982
29	30	9/16/14	1263.5	27	45.697
32	30	8/20/14	1400.9	24.9999	38.181
32	30	8/28/14	1158.6	24.9999	49.525
32	30	9/2/14	1278.8	29.0001	45.334
32	28	9/3/14	1039.8	30	57.702
32	27	9/4/14	1223.3	27	45.872
33	29	8/26/14	1070.2	27	53.544
33	30	8/28/14	967.27	30	62.03
33	30	9/3/14	1252.5	24	41.7
33	29	9/4/14	1276.8	23.0001	38.096

Appendix P: ECT Study Tables

	ECT (033)		Control (Dana0089)		
Test Name	meanRT (M)	meanRT (SD)	meanRT (M)	meanRT (SD)	z-test result
CSL1	1610.371	201.005	989.150	279.680	0.00000
PRT1	716.143	56.614	545.660	125.080	0.00031
RT1	386.989	29.238	282.620	56.495	0.00000
RT2	422.440	31.897	269.180	68.975	0.00000

		ECT (032)		Control (69117337)	
Test Name	meanRT (M)	meanRT (SD)	meanRT (M)	meanRT (SD)	t-test result
CSL1	1965.525	**227.219**	1618.250	**41.790**	0.07316
PRT1	836.656	**54.642**	746.360	**18.625**	0.05751
RT1	485.169	**80.520**	372.290	**2.249**	0.08960
RT2	516.505	75.202	384.650	1.301	0.04518

		ECT (029)		Control (Dana0858)	
Test Name	meanRT (M)	meanRT (SD)	meanRT (M)	meanRT (SD)	z-test result
CSL1	*1734.794*	**221.521**	*1967.200*	**502.360**	0.06424
PRT1	*771.502*	**82.464**	*862.560*	**269.600**	0.17669
RT1	485.434	99.178	383.200	53.751	0.00000
RT2	499.610	78.314	320.270	96.203	0.00000

	ECT (028)		Control (C003)		
Test Name	meanRT (M)	meanRT (SD)	meanRT (M)	meanRT (SD)	t-test result
CSL1	2965.700	139.678	NaN	NaN	NaN
PRT1	1191.136	92.771	889.133	76.641	0.00000
RT1	572.280	**52.184**	565.829	**81.327**	0.84286
RT2	607.540	47.212	445.650	0.000	0.01439

	ECT (027)		Control (Dana0040)		
Test Name	meanRT (M)	meanRT (SD)	meanRT (M)	meanRT (SD)	z-test result
CSL1	2126.295	214.025	1758.200	474.300	0.00027
PRT1	1095.155	91.142	674.190	102.300	0.00000
RT1	683.522	64.589	460.980	84.315	0.00000
RT2	676.489	62.005	389.880	44.333	0.00000

	ECT (025)		Control (Dana0002)		
Test Name	meanRT (M)	meanRT (SD)	meanRT (M)	meanRT (SD)	z-test result
CSL1	1736.573	353.819	1197.600	372.250	0.00000
PRT1	735.200	**78.489**	684.750	**137.530**	0.22374
RT1	445.509	61.483	298.320	52.186	0.00000
RT2	486.956	71.272	292.730	37.354	0.00000

	ECT (024)		Control (Dana0137)		
Test Name	meanRT (M)	meanRT (SD)	meanRT (M)	meanRT (SD)	z-test result
CSL1	3060.725	285.128	1349.100	439.660	0.00000
PRT1	1134.135	227.958	561.380	75.788	0.00000
RT1	627.500	20.903	357.230	42.111	0.00000
RT2	594.220	50.137	295.950	38.095	0.00000

	ECT (023)		Control (70248881)		
Test Name	meanRT (M)	meanRT (SD)	meanRT (M)	meanRT (SD)	t-test result
CSL1	2333.100	206.878	1712.250	99.631	0.01142
PRT1	1183.800	127.263	712.905	134.923	0.00417
RT1	596.400	70.821	308.185	22.436	0.00165
RT2	585.208	16.688	305.875	6.541	0.00000

	ECT (021)		Control (Dana0018)		
Test Name	meanRT (M)	meanRT (SD)	meanRT (M)	meanRT (SD)	z-test result
CSL1	*1315.495*	240.431	*1512.700*	397.420	0.01140
PRT1	*656.662*	**80.890**	*672.940*	**139.840**	0.55282
RT1	362.009	**36.717**	350.680	**45.572**	0.20493
RT2	*357.614*	28.389	*378.950*	54.127	0.04443

		ECT (020)		Control (Dana0042)	
Test Name	meanRT (M)	meanRT (SD)	meanRT (M)	meanRT (SD)	z-test result
CSL1	2366.775	237.447	1924.600	405.260	0.00001
PRT1	1010.726	125.624	864.660	123.120	0.00000
RT1	531.426	87.717	381.200	100.940	0.00000
RT2	510.595	100.357	366.770	41.411	0.00000

	ECT (019)		Control (Dana0125)		
Test Name	meanRT (M)	meanRT (SD)	meanRT (M)	meanRT (SD)	z-test result
CSL1	2200.200	**230.596**	2156.400	**363.240**	0.78745
PRT1	*845.124*	**72.175**	*951.810*	**188.160**	0.20485
RT1	*489.208*	**48.120**	*491.550*	**90.749**	0.95398
RT2	*503.584*	**31.834**	*546.150*	**104.840**	0.36395

	ECT (010)		Control (Dana0006)		
Test Name	meanRT (M)	meanRT (SD)	meanRT (M)	meanRT (SD)	z-test result
CSL1	*1309.376*	**146.159**	*1471.700*	**457.680**	0.14365
PRT1	715.435	**50.757**	608.000	**306.660**	0.14860
RT1	400.791	36.477	273.750	66.687	0.00000
RT2	415.775	26.967	245.750	35.735	0.00000

	ECT (006)		Control (Dana0024)		
Test Name	meanRT (M)	meanRT (SD)	meanRT (M)	meanRT (SD)	z-test result
CSL1	1864.550	184.223	1372.500	366.290	0.00722
PRT1	779.190	63.073	614.660	166.110	0.04759
RT1	389.010	19.351	305.180	78.474	0.03264
RT2	381.280	25.806	247.350	40.572	0.00000

	ECT (005)		Control (Dana0092)		
Test Name	meanRT (M)	meanRT (SD)	meanRT (M)	meanRT (SD)	z-test result
CSL1	*1716.963*	**177.738**	*2437.200*	**522.310**	0.00010
PRT1	*735.449*	**44.278**	*1013.400*	**226.350**	0.00023
RT1	*403.280*	50.902	*420.730*	48.884	0.28421
RT2	427.618	53.860	394.150	60.315	0.09598

	ECT (003)		Control (Dana0110)		
Test Name	meanRT (M)	meanRT (SD)	meanRT (M)	meanRT (SD)	z-test result
CSL1	1920.007	302.651	1887.300	432.170	0.55773
PRT1	872.792	147.258	753.030	131.930	0.00000
RT1	487.297	77.091	383.820	53.380	0.00000
RT2	544.540	67.310	431.050	59.246	0.00000

	ECT (002)		Control (Dana0009)		
Test Name	meanRT (M)	meanRT (SD)	meanRT (M)	meanRT (SD)	z-test result
CSL1	*1236.627*	**127.691**	*1292.000*	**440.440**	0.55540
PRT1	667.795	43.626	575.780	82.710	0.00000
RT1	*332.702*	**14.435**	*347.320*	**44.398**	0.12251
RT2	*337.151*	**16.561**	*387.050*	**140.820**	0.09651

	ECT (001)		Control (Dana0091)		
Test Name	meanRT (M)	meanRT (SD)	meanRT (M)	meanRT (SD)	z-test result
CSL1	2449.031	320.750	1949.600	471.360	0.00013
PRT1	1014.382	159.866	642.530	109.820	0.00000
RT1	597.178	68.127	309.400	34.900	0.00000
RT2	597.310	58.634	296.520	33.491	0.00000

Appendix Q

Home-based TeleMental Health for Rural Veterans

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Director, National Center for PTSD, Pacific Islands Division

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In collaboration with:

- US Department of Veterans Affairs:
  - Laurel King, PhD
  - National Center for PTSD Research Team
- Anthrotronix Inc, Bethesda MD
  - Cori Lathan, PhD
  - Anthrotronix Team

Disclosures

- None to disclose.

Support

- This project was supported by:
  - US Department of Veterans Affairs
    - Office of Rural Health
    - National Center for PTSD
  - Department of Defense
    - Congressionally Directed Medical Research Program, Rapid Innovation Fund
    - Through a subcontract with Anthrotronix, Inc.

- Views expressed in this presentation are that of the presenter, and not of the U.S. Department of Defense or the U.S. Department of Veterans Affairs.

Learning Objectives

By the end of the session:

- The participant will recognize the value of home-based telemental health for rural veterans with PTSD compared to in-clinic treatment.
- The participant will be able to discuss the value of home-based telehealth for improving emotional and neurocognitive functioning in rural veterans with PTSD.
- The participant will be able to report what factors do not improve due to a brief intervention for rural veterans with PTSD using home-based telehealth.

Problem

- Rural veterans, like others living in rural areas, are underserved for medical specialties
- The VA in particular has had unacceptable wait times for veterans who require evidence-based treatment for PTSD
- Providers at VA Clinical Based Outpatient Clinics (CBOCs) are either not trained in EBTs for PTSD or are too busy with other patients to be able to devote weekly or twice-weekly sessions, as is standard of care
- Travel to clinics can be prohibitive
  - Time to travel in rural areas
  - Cost to travel (island to island)
  - Physical and psychological limitations

Problem

- Prior research has shown that tele-mental health is equivalent in most ways to in-clinic mental health treatment for rural veterans
- This research has been conducted from one clinic to another remote clinic or from one room to another to demonstrate the effect
  - Morland et al (2011). Group cognitive processing therapy delivered to veterans via telehealth: A pilot cohort. Journal of Traumatic Stress, 24(4), 465-9.
  - Morland et al (2010). Telemedicine for anger management therapy in a rural population of combat veterans with posttraumatic stress disorder: a randomized noninferiority trial. J Clinical Psychiatry: 71(7):855-63.
  - Morland et al (2014). Cognitive processing therapy for posttraumatic stress disorder delivered to rural veterans via telemental health: a randomized noninferiority clinical trial. J Clinical Psychiatry;75(5):470-6.

Problem

- However, many Veterans have difficulty getting care at Community Based Outpatient Clinics (CBOCs).
  - Scheduling is difficult: matching at time when the Telehealth room is available
  - Traveling to the VA-CBOC
    - For physically or psychologically injured Veterans
    - Travel from rural areas can be prohibitive due to transportation, time, cost
  - No-show and drop-out rates are very high (up to 50%).

Solution

- Home-based Telehealth:
  - Connects therapists with expertise in treating veteran PTSD with rural veterans who otherwise have difficulty obtaining state of the art care

Challenges

- Many rural veterans:
  - Did not have high speed internet
  - Did not have a computer or tablet
  - Or did not feel comfortable using them
- The VA did not have a home-based program
  - When they did launch home-based care, it was using a system that was quirky (MOVI/JABBR)
    - Needed downloads prior to every session
    - Frequent dropped calls

Challenges

- Federal Gov't requires very secure connection (FIPS 140-2)
- Cannot email patient information
  - difficult to review homework
- Does not like to loan out equipment
- Purchasing IT equipment is very difficult
  - for providers
  - for patients
- Contracting with service providers is difficult (Verizon)

Challenges

- Confidentiality
  - Verbal (document in medical records)
  - Signed (causes delay)
- Safety
  - What if they state intention to harm
  - What if they demonstrate physical or psychological distress

Program

- $1M 3-year demonstration grant to the VA Office of Rural Health
  - Staff:
    - 2.0 FTE Clinical Psychologists
    - 1.5 FTE Psychology Technicians (MA)
  - 40, 4G enabled,10-inch Samsung Galaxy Tablets
  - Laptop computers for the clinicians
  - Vidyo videoconferencing software
  - Verizon contract

Treatment

- CPTc - Cognitive Processing Therapy (cognitive only)
  - Referals from primary MH provider
    - We did not want to do intakes and manage their overall care
  - Screening for appropriateness prior to treatment
  - (preliminary SUD or other treatment if necessary)
  - Orientation session (tablets, therapy, consents, assessments)
  - 12 twice-weekly sessions
  - Referral back to their primary MH provider
  - Monthly follow-up calls as needed

Progress

- Year 1 – set up and piloting
- Year 2 – 900 patient encounters
  - Oahu (Waianae; North Shore)
  - Maui, Kauai, Hawaii, Molokai, Guam, Saipan
- Year 3 – in progress
  - Expanding to include any post-traumatic symptomology
    - Anxiety, Depression, Anger, Post-traumatic Numbing, Insomnia, Somatic complaints

Criteria

- No intent to harm within past six months
- No active or immediate potential for psychosis
- SUD
  - Must guarantee to be sober during sessions
  - No more than 4 drinks/day, and encouraged to reduce
  - No major psychoactive recreational substances
- Must have ability to commit to schedule
- Must have isolated quiet room for sessions
- May require Personal Safety Person (PSP), if risk is elevated or they are in a remote area
- Must have ermergency response team within 15 minutes of session location

Procedure

- Receive referral
- Contact veteran
  - Describe program
  - Describe treatment
  - Obtain verbal agreement
- Send out consent and HIPAA forms
- Veteran signs and return consents and Baseline Assessments
- Send out tablet, procedure guide, and CPT manual to vet

Procedure

- Psych tech orients veteran to tablet/Vidyo, assessments
  - Using 4G Verizon network or WiFi if 4G not available
- Psych tech schedules therapy sessions
- Psych tech Vidyo-calls veteran five minutes prior to each session to insure connectivity.
- Therapist ‘joins’ call, psych tech drops out
- Continues for orientation and 12 CPT sessions
- Mid and Final Assessments

Assessment

- $700,000 grant from the Department of Defense as part of a grant to Anthrotronix, Inc, Silver Springs, MD
- Assess:
  - Emotional Distress (PCL, PHQ, PSQI)
  - Neurocognitive Functioning (DANA, NBSI-22)
  - Familiarity and Comfort with Technology
- Groups:
  - Of all those interested in and enrolled in treatment
  - (We also sought a comparison group who were eligible but not interested in this approach to treatment and sought in-clinic treatment; however, only 2 preferred clinic Tx/HBTx)

Assessment

- VA IRB Approved protocol established to examine outcome
- Assessments:
  - Baseline (prior to treatment initiation)
  - Mid-treatment (at 3-4 weeks, independent of #sessions)
  - Post-treatment (1-week; 7-10 weeks, independent of #sessions)
- Analysis
  - Included only those who had completed all three assessments
  - Intention-to-treat: included all those who initiated treatment, even if they dropped out prior to completion (as long as they were able to complete assessments).

Interim Analysis

Emotional Factors

Neurocognitive Functioning

Drop-outs

No-shows

Comfort levels with technology

Demographics

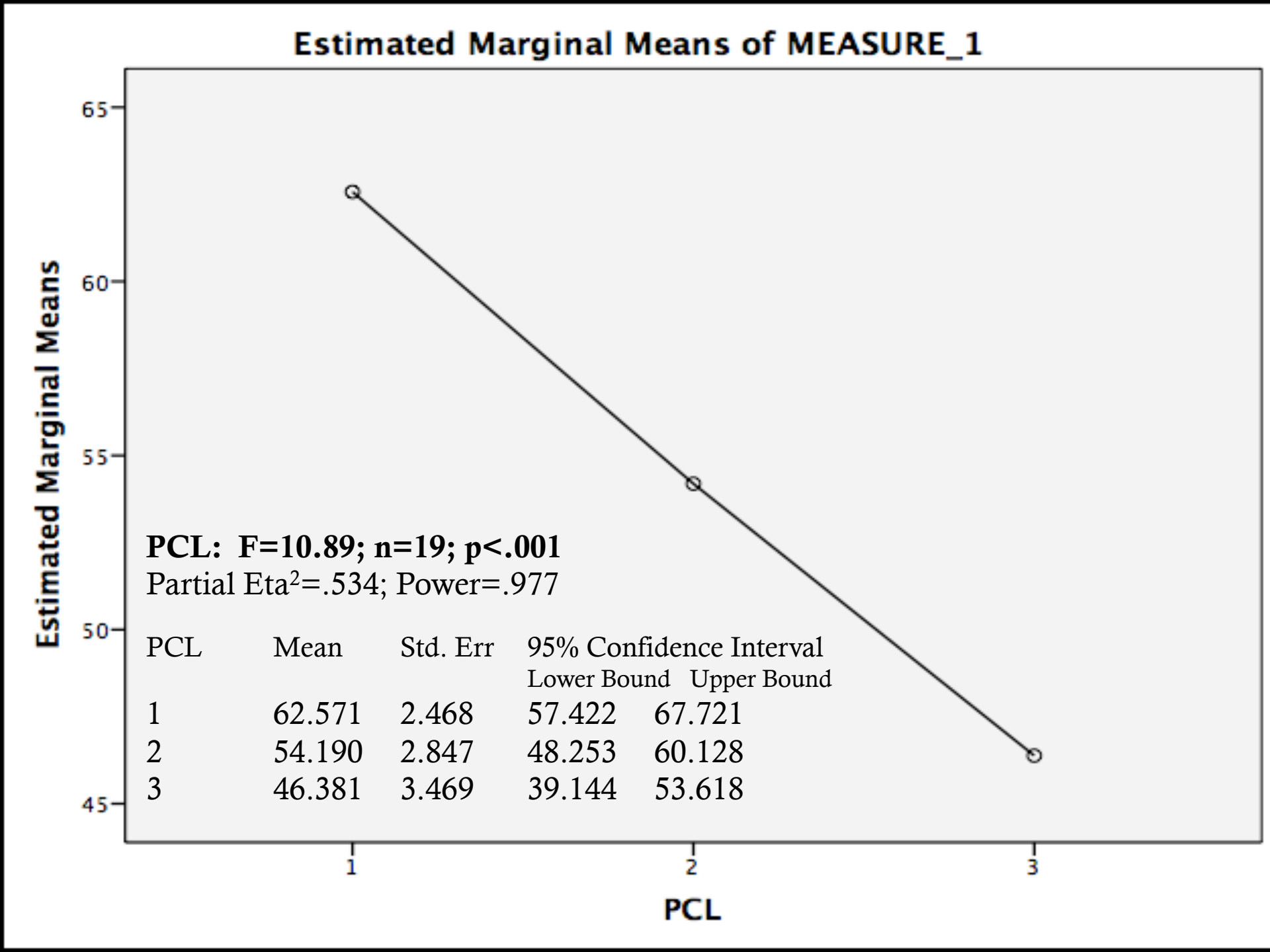
- 78.7% Male (3 didn't indicate)
- 74.5% deployed within the past five years

Ethnic group identifies with

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	White	13	27.7	31.0	31.0
	Black	3	6.4	7.1	38.1
	Asian American	6	12.8	14.3	52.4
	Pacific Islander	13	27.7	31.0	83.3
	Mixed	3	6.4	7.1	90.5
	Other	4	8.5	9.5	100.0
	Total	42	89.4	100.0	
Missing	System	5	10.6		
Total		47	100.0		

Demographics

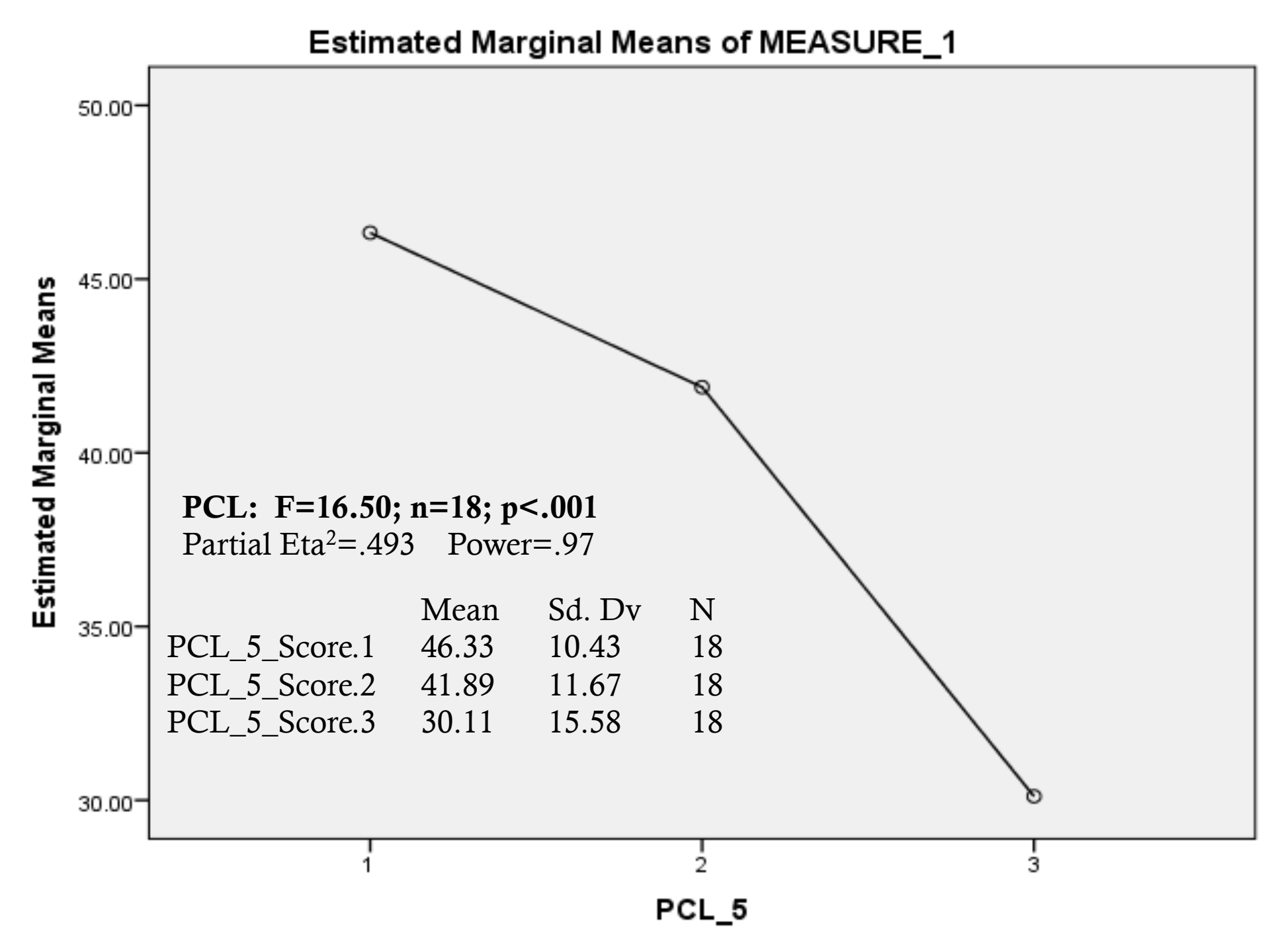
- 38.3% had a blast/explosion to the head
- 97.9% had received a PTSD Dx (Dx upon study entry)
- 68% Depression Dx
- 40.4% Anxiety Disorder Dx
- 25.5% Have tried to kill self (60% within past 4 years)
- 70.2% Have hit in anger
- 23.5% Have been hospitalized for MH problem
  - 50% of these within past 3 years
- 32% had more than 3 concussions
- 68.1% has chronic pain
- 55.3% has sleep problems
  - 29.8% Insomnia Dx



PCL: F=10.89; n=19; p<.001

Partial Eta^2=.534; Power=.977

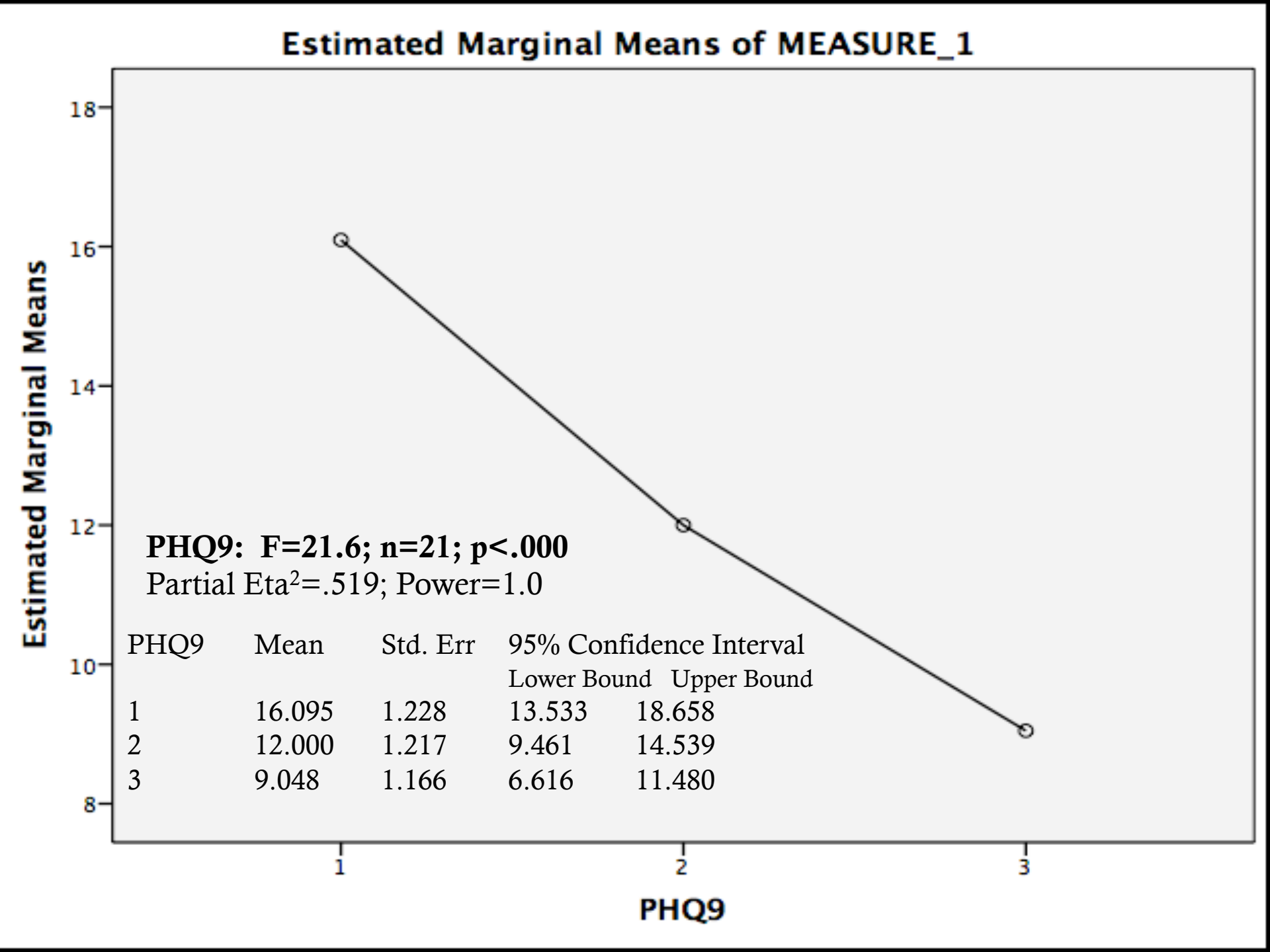
PCL	Mean	Std. Err	95% Confidence Interval	
			Lower Bound	Upper Bound
1	62.571	2.468	57.422	67.721
2	54.190	2.847	48.253	60.128
3	46.381	3.469	39.144	53.618



PCL: F=16.50; n=18; p<.001

Partial Eta^2=.493 Power=.97

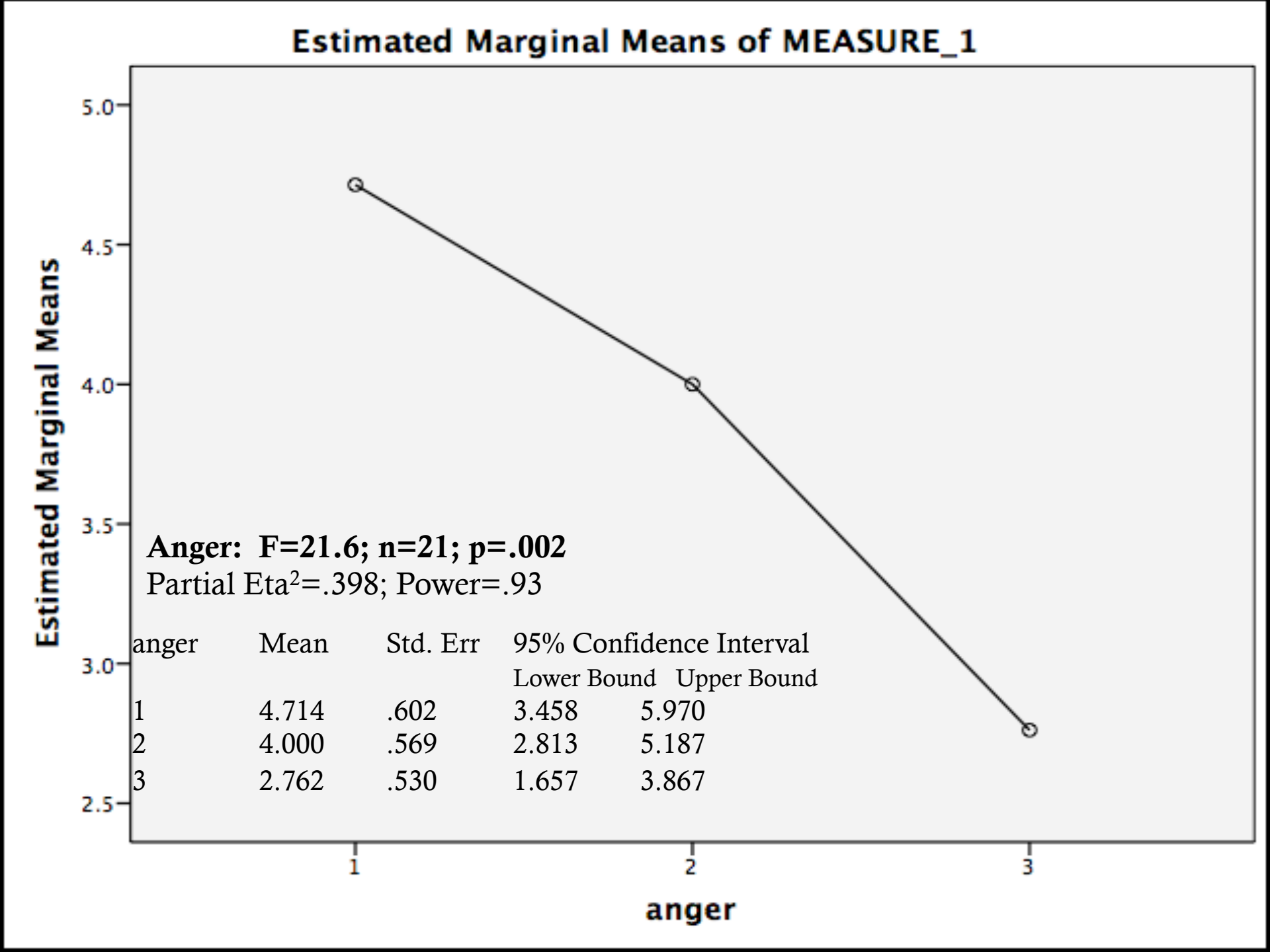
	Mean	Sd. Dv	N
PCL_5_Score.1	46.33	10.43	18
PCL_5_Score.2	41.89	11.67	18
PCL_5_Score.3	30.11	15.58	18



PHQ9: F=21.6; n=21; p<.000

Partial Eta^2=.519; Power=1.0

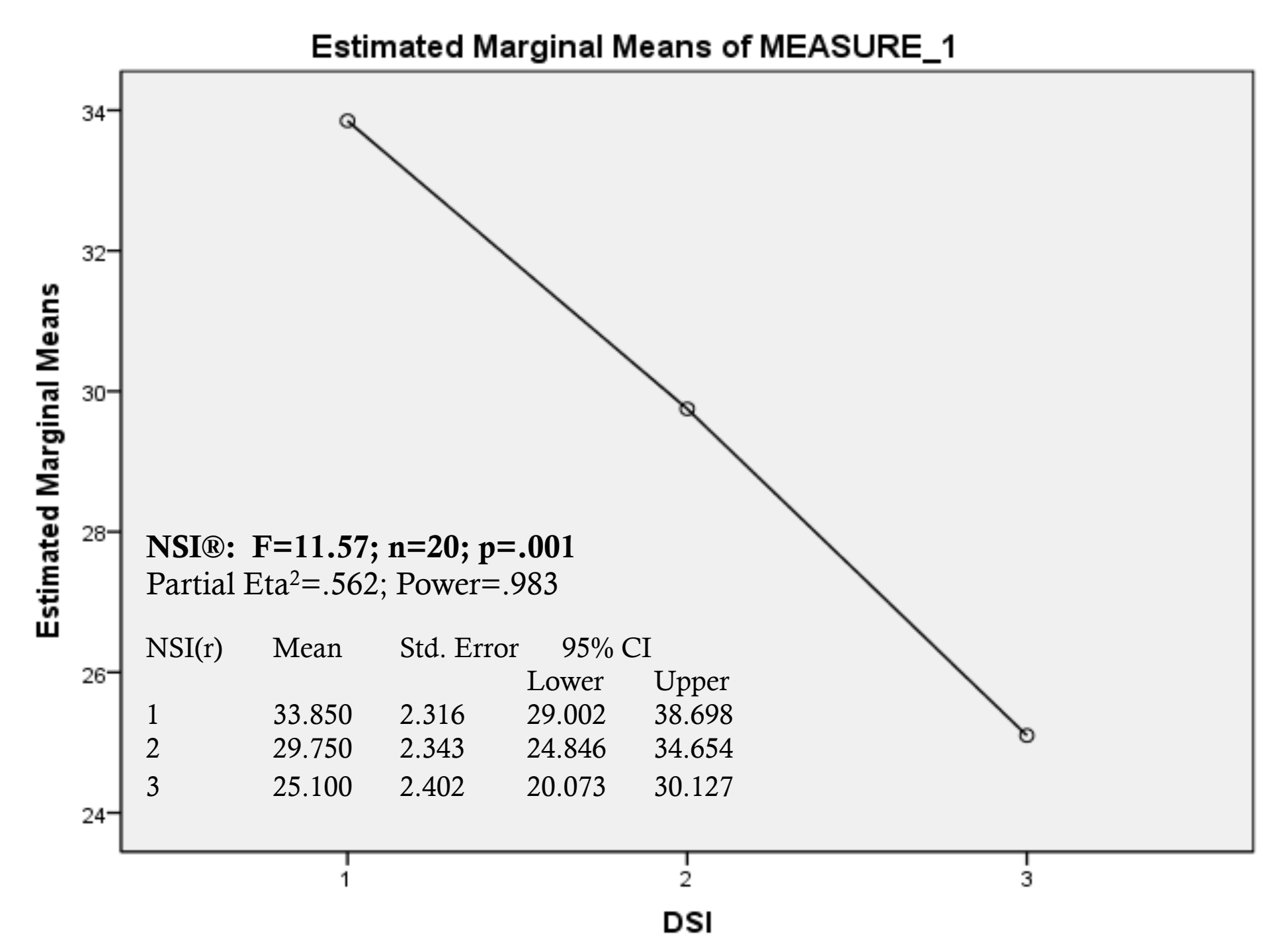
PHQ9	Mean	Std. Err	95% Confidence Interval	
			Lower Bound	Upper Bound
1	16.095	1.228	13.533	18.658
2	12.000	1.217	9.461	14.539
3	9.048	1.166	6.616	11.480



Anger: F=21.6; n=21; p=.002

Partial Eta^2=.398; Power=.93

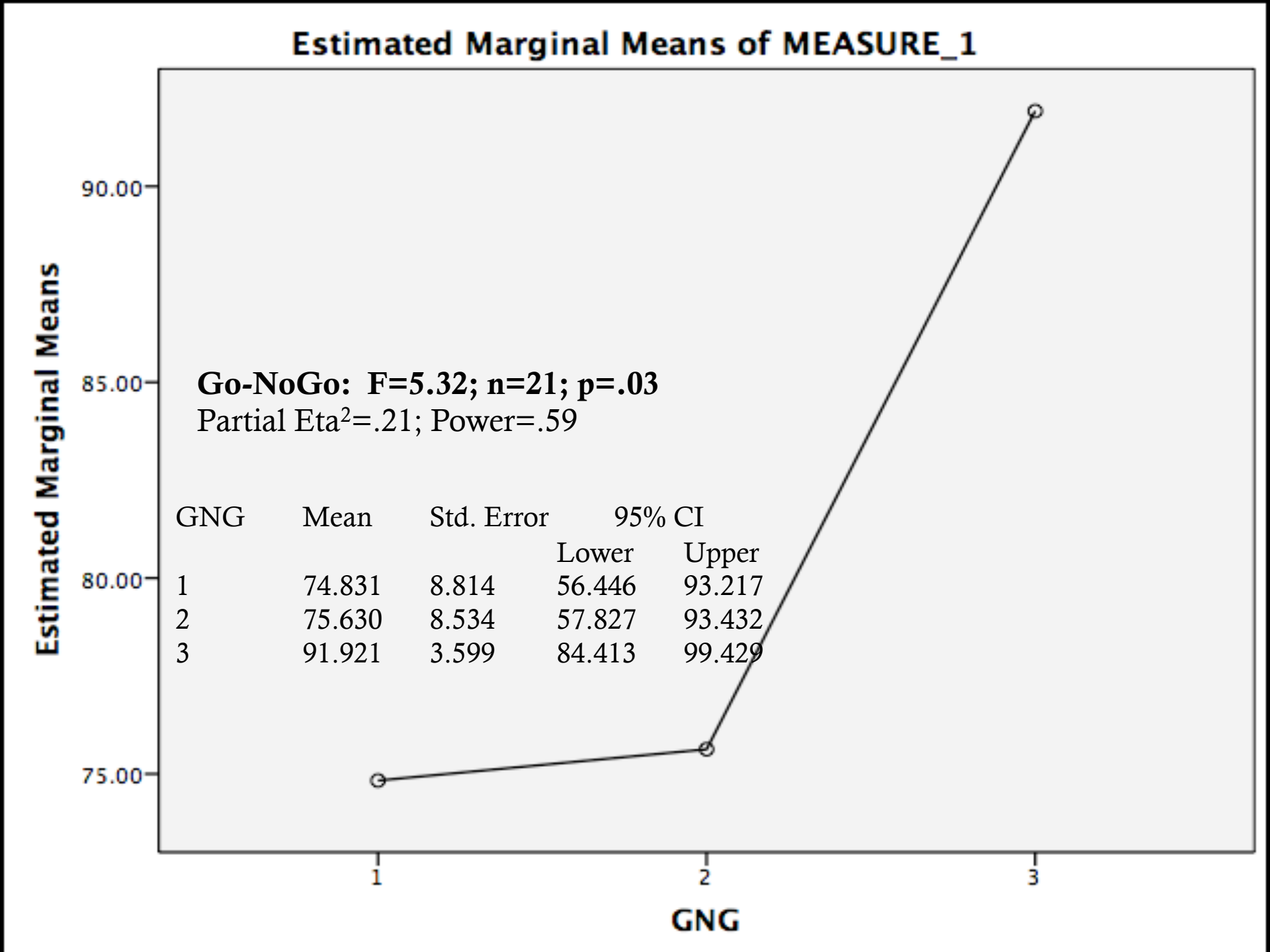
anger	Mean	Std. Err	95% Confidence Interval	
			Lower Bound	Upper Bound
1	4.714	.602	3.458	5.970
2	4.000	.569	2.813	5.187
3	2.762	.530	1.657	3.867



NSI®: F=11.57; n=20; p=.001

Partial Eta^2=.562; Power=.983

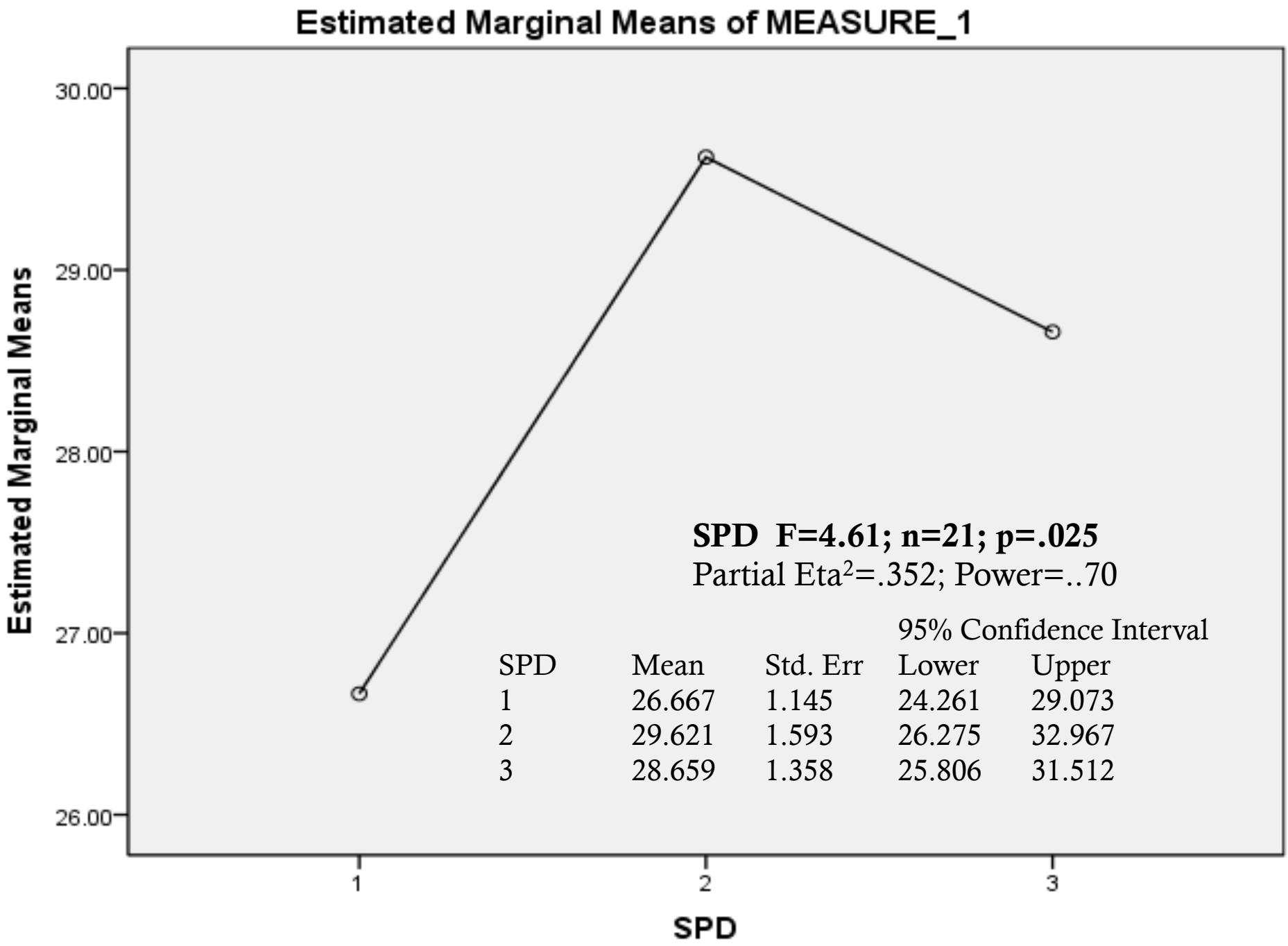
NSI(r)	Mean	Std. Error	95% CI	
			Lower	Upper
1	33.850	2.316	29.002	38.698
2	29.750	2.343	24.846	34.654
3	25.100	2.402	20.073	30.127



Go-NoGo: F=5.32; n=21; p=.03

Partial Eta^2=.21; Power=.59

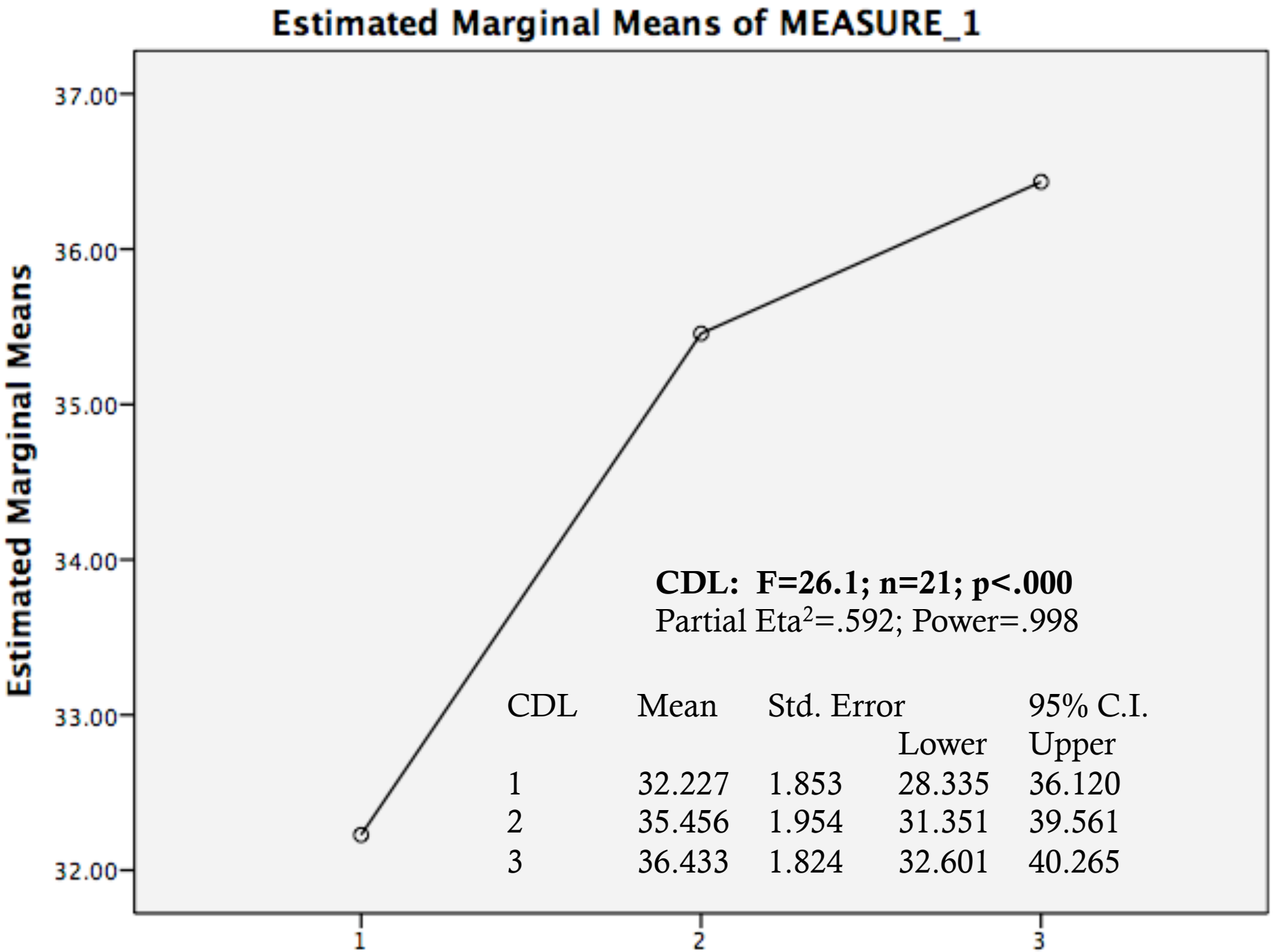
GNG	Mean	Std. Error	95% CI	
			Lower	Upper
1	74.831	8.814	56.446	93.217
2	75.630	8.534	57.827	93.432
3	91.921	3.599	84.413	99.429



SPD F=4.61; n=21; p=.025

Partial Eta^2=.352; Power=..70

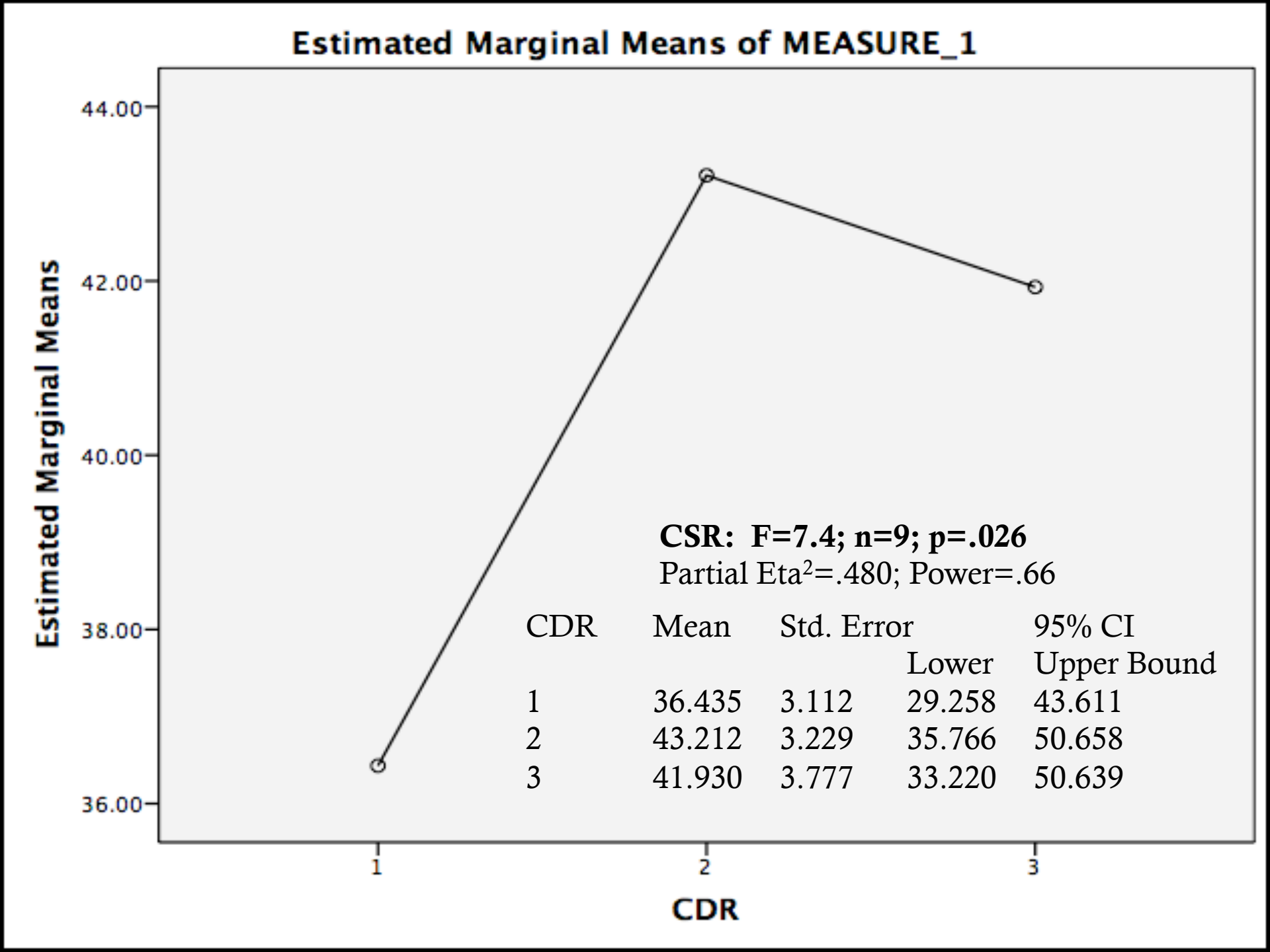
SPD	Mean	Std. Err	95% Confidence Interval Lower	Upper
1	26.667	1.145	24.261	29.073
2	29.621	1.593	26.275	32.967
3	28.659	1.358	25.806	31.512



CDL: F=26.1; n=21; p<.000

Partial Eta^2=.592; Power=.998

CDL	Mean	Std. Error	95% C.I.	
			Lower	Upper
1	32.227	1.853	28.335	36.120
2	35.456	1.954	31.351	39.561
3	36.433	1.824	32.601	40.265



CSR: F=7.4; n=9; p=.026

Partial Eta^2=.480; Power=.66

CDR	Mean	Std. Error	95% CI	
			Lower	Upper Bound
1	36.435	3.112	29.258	43.611
2	43.212	3.229	35.766	50.658
3	41.930	3.777	33.220	50.639

No Improvement Found

- Insomnia (PSQI)
  - Possibly insomnia (Mean=12 on PSQI) is slower to recover
- Simple Reaction Time
- Procedural Reaction Time
  - SRT and PRT are more indicative of white matter function
  - GNG-impulsivity; CDL-attention; CDR-STM; SPD are indicative of executive functioning
- Perhaps physiological changes are slower to occur, requiring continued treatment (or longer follow-up).
- Other studies have not examined neurocognitive changes due to treatment of PTSD, so difficult to compare.

Other changes

- About 18% drop-outs
- Much better than is found in CBOCs with PTSD patients (which can run as high as 50%)
- Low no-show rate (hard to no-show when one is at home)
- Saving on travel
- Veterans typically seen within two weeks of referral
- Very high patient satisfaction with Tx and technology
- Willing to see future MH professionals via HBTH
- Willing to see other healthcare professionals via HBTH

How did Veterans feel about Home-based Telemental Health?

10. Assuming the doctor believes either option is fine, which would you prefer?

a. For mental health issues:

MID	Prefers this mode for MH issues			Total
	Going to clinic to receive F2F with Dr.	Home-based televideo with Dr	Doesn't matter to me	
Total	3	12	13	28

b. For physical health follow-up sessions:

MID	Prefers this mode for physical health follow up sessions			Total
	Going to clinic to receive F2F with Dr.	Home-based televideo with Dr	Doesn't matter to me	
Total	11	8	10	29

I am comfortable interacting with the provider on the computer/webcam/tablet

MID	comfortable interacting with the provider on the computer / webcam / tablet.		Total
	Agree	Strongly Agree	
Total	17	13	30

T8). I feel I have the same level of rapport with my MH Provider when participating in HBTMH as I do in face-to-face appointments.

MID	same level of rapport with my HBMTH Provider as I do in face-to-face appointments.				Total
	Disagree	Neutral	Agree	Strongly Agree	
Total	2	3	13	12	30

Next Steps

- Sustainment hoped for
  - Expecting that VA will put more emphasis into home-based telemental health, including sending out tablets when necessary
  - We have showed that the cost to deliver HBTMH for veterans with PTSD is far less than the benefits received
    - Monetarily (VERA calculations of VA received to support tx)
    - Time to initial and completing treatment
- Applying for grants to determine the feasibility and effectiveness of Behavioral Health and PC integration via HBTMH

Appendix R

Analysis of Defense Automated Neurobehavioral Assessments on Two Groups of Mixed Martial Arts Fighters

Prepared by: Resnick, Chodorow, and Associates

August 18, 2014

Contents

List of Figures

List of Tables

1 Overview

The data are summaries of repeated measures of Defense Automated Neurobehavioral Assessments (DANA) on two groups of fighters. Each assessment is comprised of three tests: "go/no-go" (GNG), simple reaction time (SRT), and procedural reaction time (PRT). Within each study group, all tests were performed during the course of a single night. At the beginning of the night, each test was administered to establish pre-fight baseline measurements. After fighting began, post-baseline tests were administered to one group at a single subsequent time point, and to the other group at three subsequent time points. The results of each assessment include mean and median reaction time (RT), mean and median correct, and mean and median thruput.

There are two research questions:

1. Across the two groups of fighters, are DANA measures similar at corresponding points in time? Investigators hypothesize that (a) the distribution of the baseline measures will be similar in the two groups, and that (b) similarities in these measures will "track in parallel" at subsequent time points during the night. Thus, they expect to see no meaningful differences in measures between the two groups at a given point in time.

2. Within each of the two study groups, are DANA tests "stable" during the night? Investigators hypothesize that accumulating physical fatigue during the night will result in decrements in performance on DANA measures during the night. They expect to see similar decrements in both groups of fighters.

The remainder of this document is organized as follows. In Section 2, we provide tables and visual displays of descriptive statistics on each measure and study group, for each time point. In Section 3, we tests for differences between the two groups at baseline, and within each of the two groups over time. Finally, the descriptive statistics displayed in the figures of Section 2 are given in table format in the Appendix, along with additional summary statistics.

2 Exploratory Data Analysis

To explore part (a) of research question 1, Figure 1 shows the distribution of the DANA measures taken at baseline (time 0) for each of the study groups. Visual inspection of these plots does not reveal any striking patterns in the differences between the two study groups prior to fighting.

Figure 2 displays the distribution of DANA measures for group 1 (those who fought in Atlantic City) at baseline and at the time of the post-baseline measurement. Mean RT, RT correct, and thruput are on the y-axes, and the baseline and post-baseline measures are indicated on the x-axes with 0 and 1, respectively. For each of the three tests (SRT, PRT, and GNG), it appears that mean RT and mean RT correct are higher at time 1 versus time 0, and that mean thruput is lower at time 1 versus time 0. Similarly, Figure 3 shows the distribution of the DANA measures for group 2 (those who fought in Long Island) at baseline and at each of the three post-baseline time points (indicated with 1, 2, and 3 on the x-axes). The plots for this group do not show the same clear pattern of decline in performance over time.

To examine potential time effects more closely, Figures 4 and 5 display the distributions of paired differences for each measure and study group at each time point. Specifically, Figure 4 displays the distribution of each assessment measure taken on group 1 at time 1, minus the corresponding measure taken at base-

line[1]. Figure 5 displays the distribution of each assessment measure taken on group 2 at time t minus the corresponding measure taken at time 0, for $t = 1$, 2, and 3 (indicated on the x-axes). In each of these plots, a difference of zero (no difference over time) is indicated with a horizontal red line. The paired differences in Figure 4 give strong visual support for the hypothesis that performance declines over time. Each of the medians (thick, black center lines) of RT and RT correct for each of the three tests lie above 0, indicating longer reaction times during the post-baseline assessment. Furthermore, all the first quartiles (bottoms of the boxes) of RT and RT correct for SRT lie above 0. Similarly, most of the paired differences in thruput fall below 0, indicating lower thruput during the post-baseline assessment. However, the plots in Figure 5 do not add support for the hypothesis of decline in performance over time. On the contrary, plots of the paired differences in PRT and GNG indicate improvement in performance over time, and the paired differences in SRT show no visual difference in performance over time.

One factor that may contribute to differences in post-baseline measures between the two study groups is a difference in testing protocol. In particular, if the post-baseline assessments for one group were taken much sooner or later after fighting than they were for the other group, it may cause differences in the results. Figure 6 displays the distribution of the time in minutes between baseline assessments and each subsequent assessment by study group. Group 1 had only one post-baseline assessment taken at an average of approximately four hours after baseline measures were established. Group 2 had three post-baseline assessments taken at averages of 19, 42, and 58 minutes, respectively, after baseline assessment. These are substantial differences and careful consideration should be given when performing statistical analyses of the two study groups in combination.

[1]The maximum difference in RT for the mean of PRT (displayed in the upper left plot of Figure 4) falls outside of the plotting region.

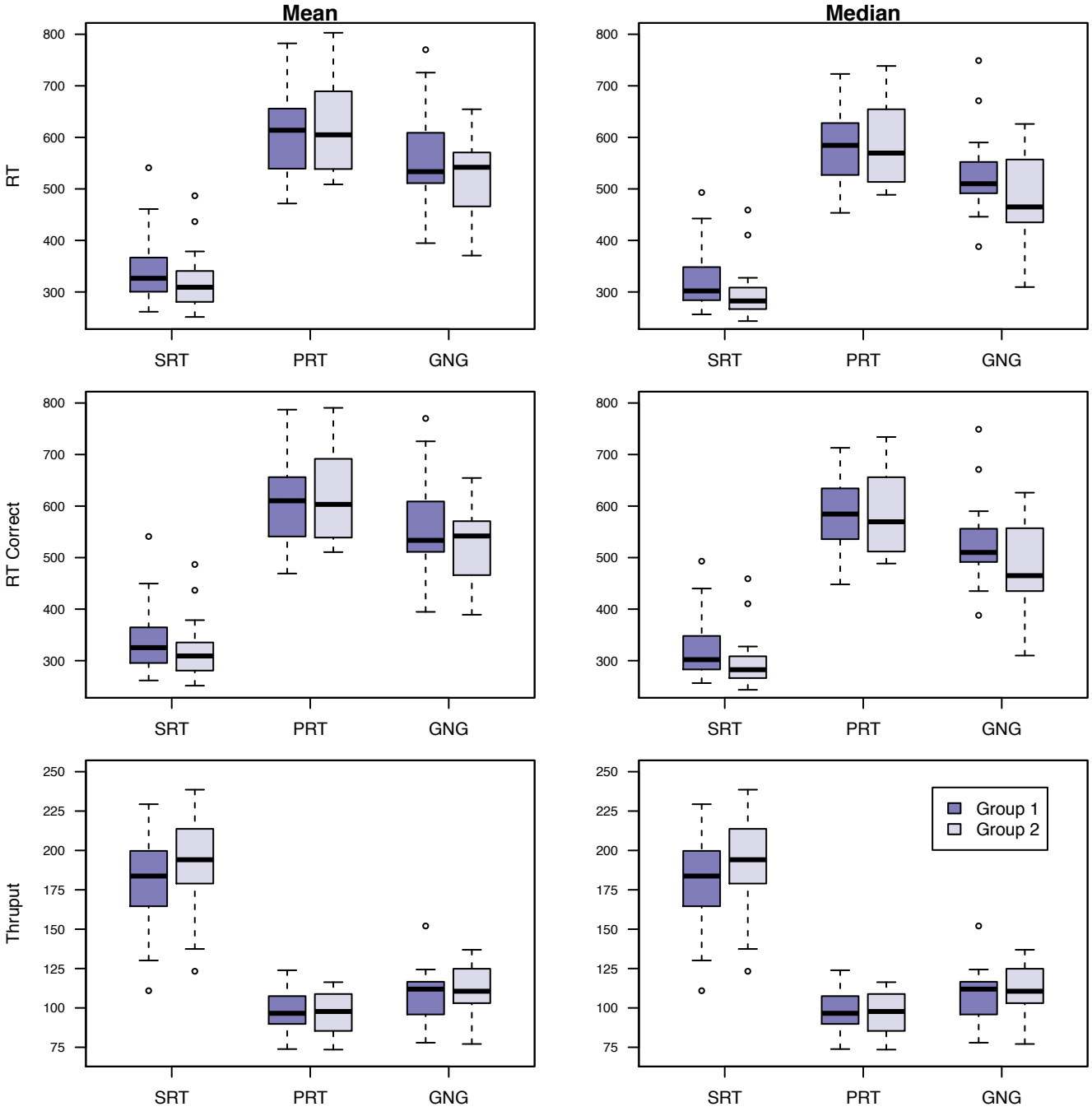


Figure 1: Distribution of Baseline DANA Measures by Study Group

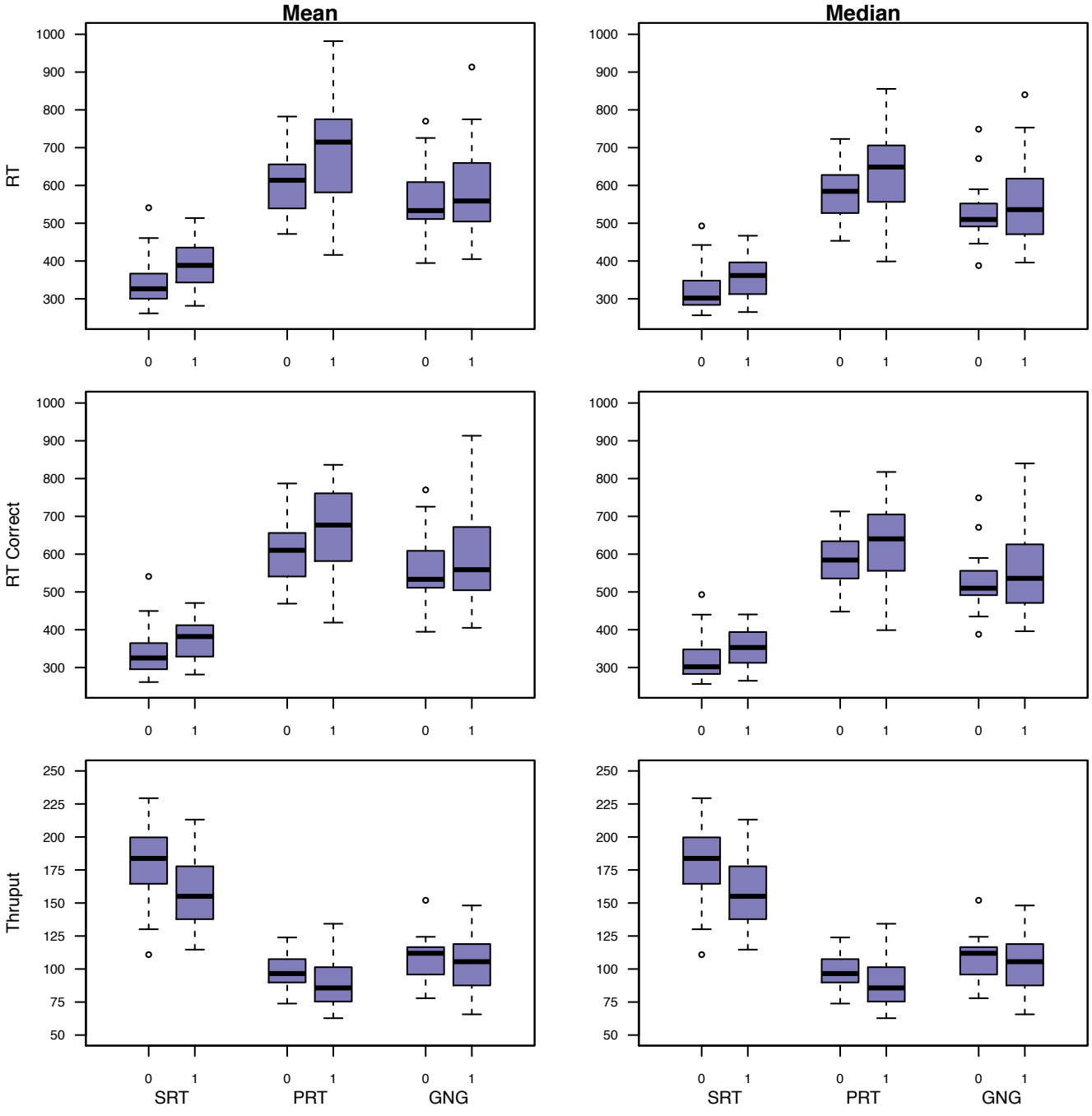


Figure 2: Distribution of Group 1 DANA Measures Over Time

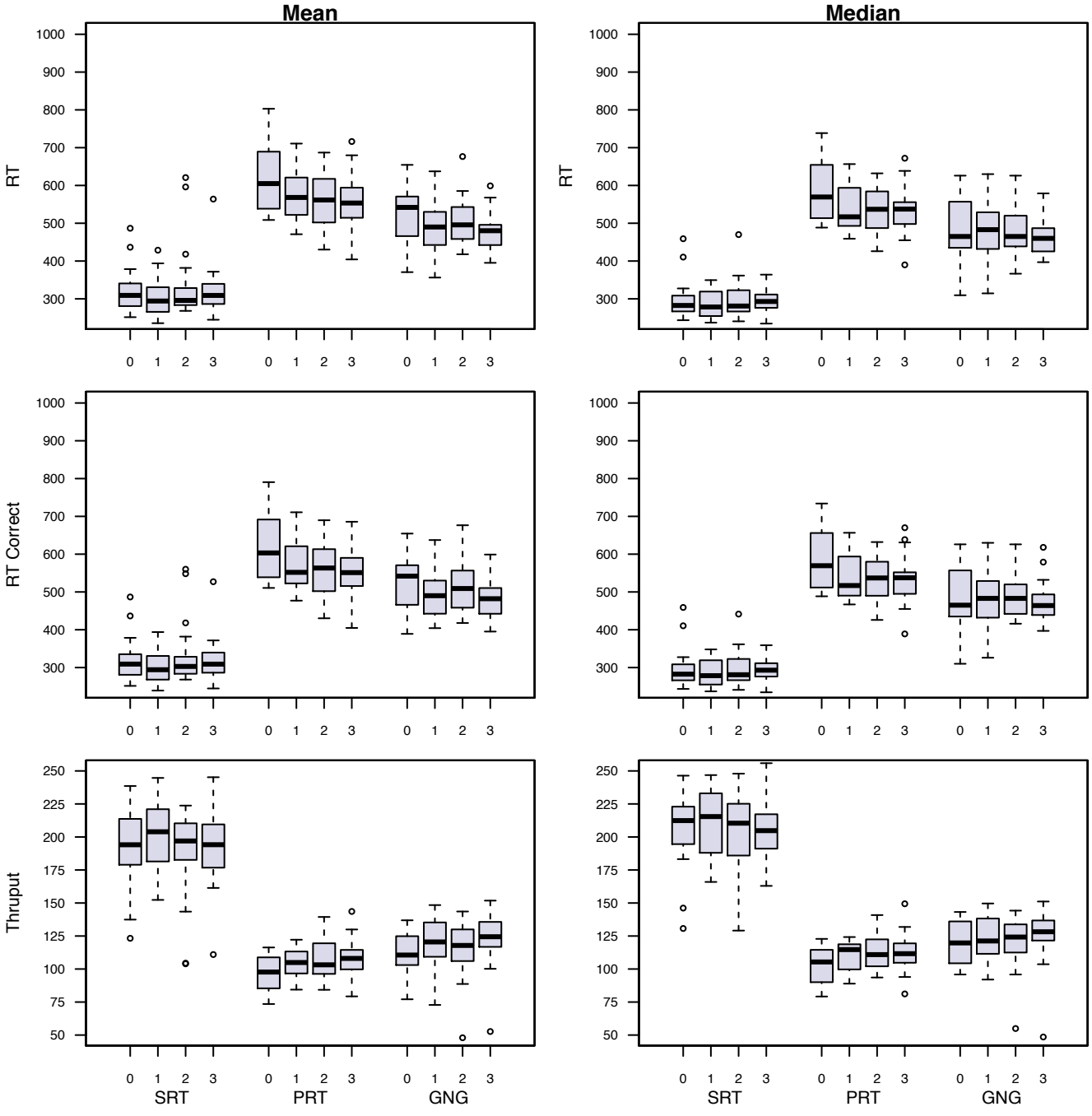


Figure 3: Distribution of Group 2 DANA Measures Over Time

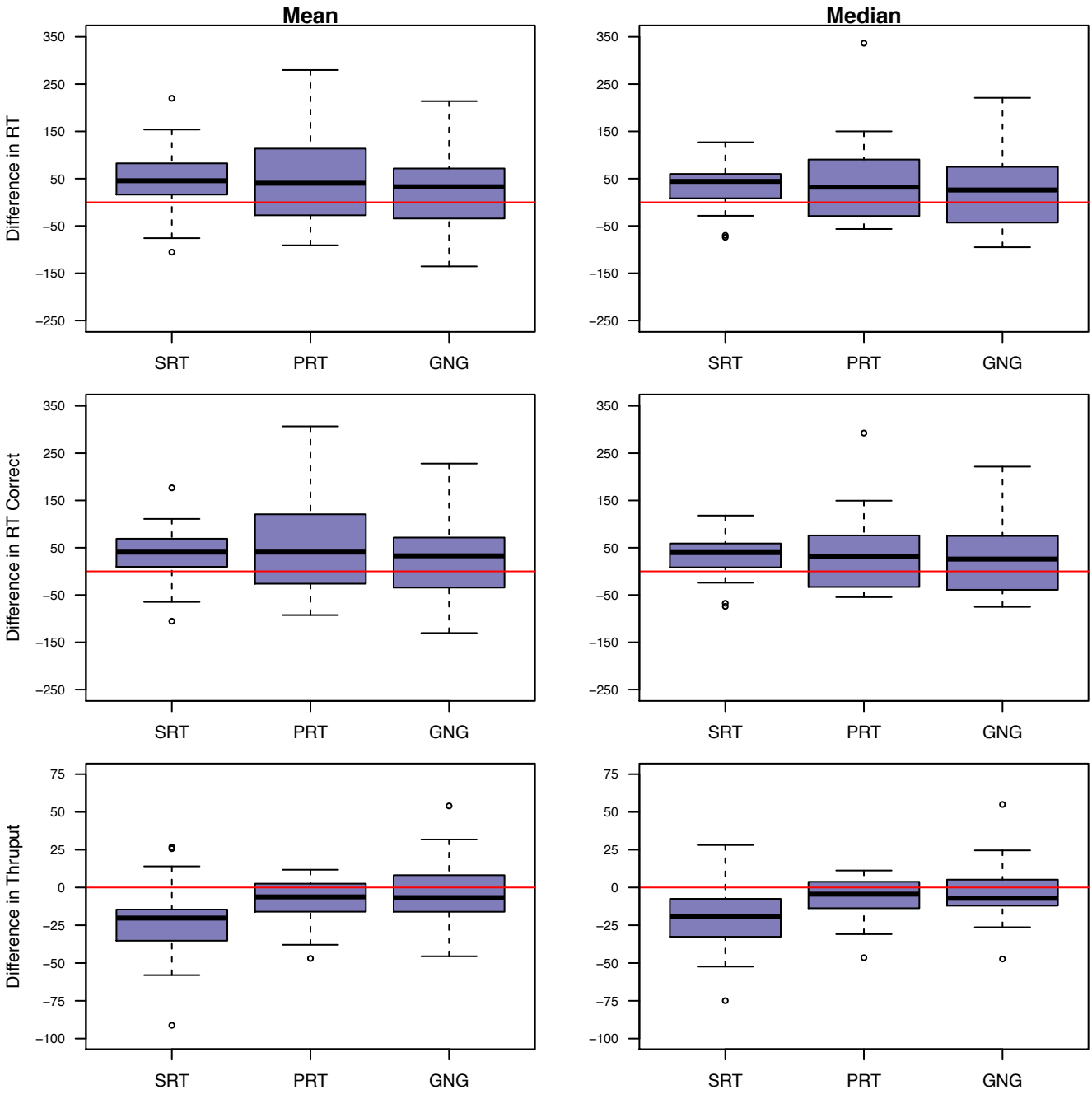


Figure 4: Differences in Group 1 DANA Measures Over Time

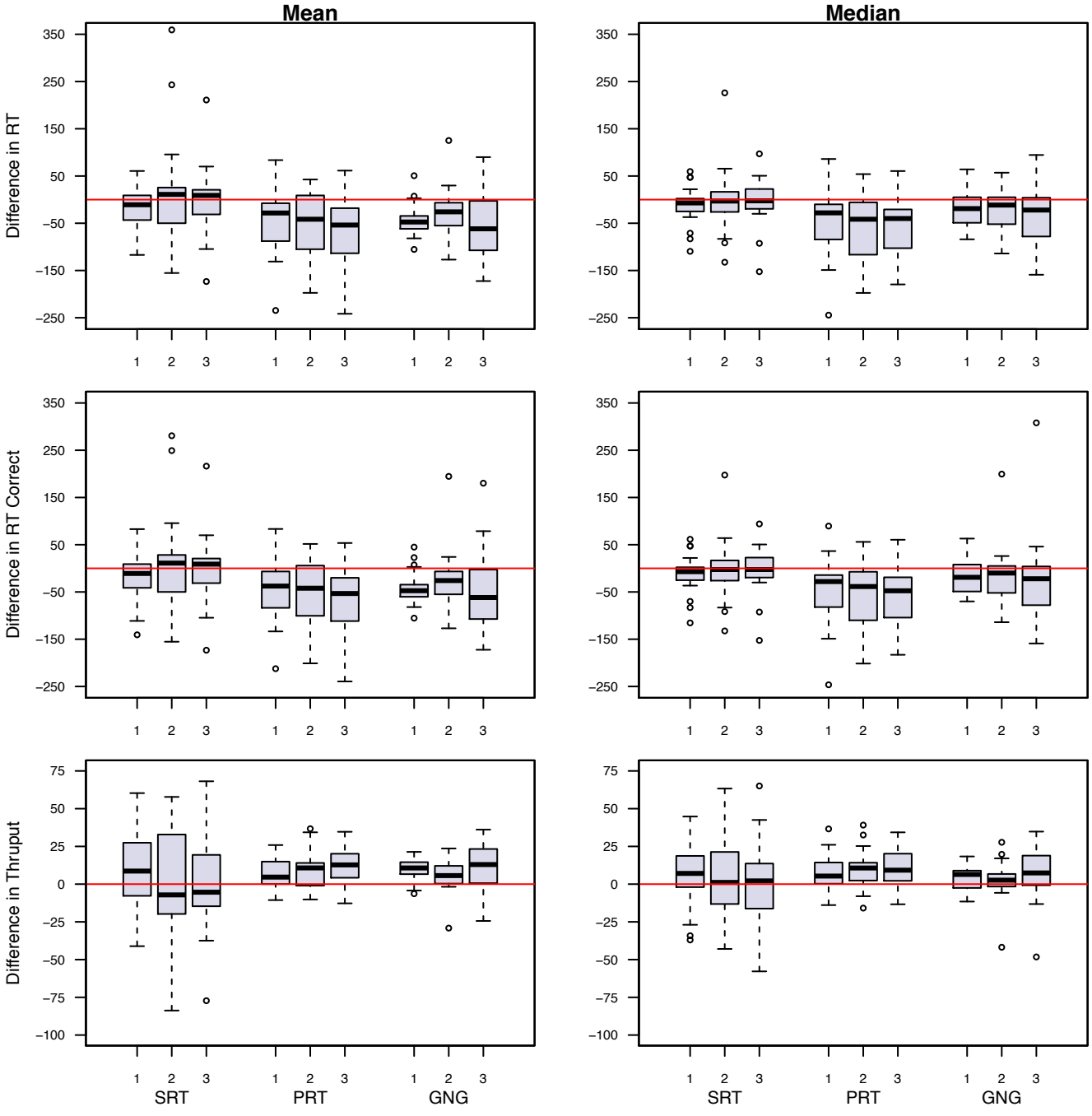


Figure 5: Differences in Group 2 DANA Measures Over Time

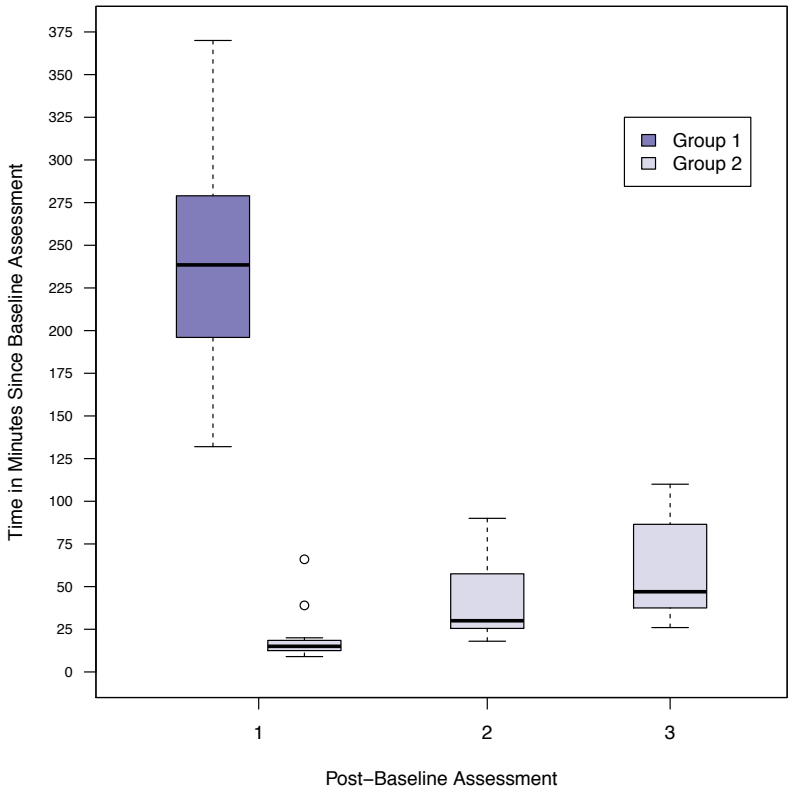


Figure 6: Distribution of the Time Between Baseline Assessment and Each Subsequent Assessment by Study Group

3 Statistical Inference

To address the research questions with more rigor, we formally test each hypothesis detailed in Section 1 with a parametric and non-parametric method.

3.1 Baseline Assessments

We begin with an examination of the DANA measures at time 0. Tables 1 and 2 display the results of two-sample t-tests and Wilcoxon rank sum tests, respectively, for differences in the two study group at baseline, for each of the eighteen measures. None of the two-sample t-tests are significant at the $\alpha = 0.05$ level, and, while three of the eighteen Wilcoxon rank sum tests have p-values less than 0.05, none of the tests are significant at the $\alpha = 0.05$ level after correcting for multiple comparisons. Thus, we conclude that there were no significant differences between DANA measures of the two study groups prior to fighting.

Table 1: Two-Sample t-Tests of Equality in the Baseline Means of Groups 1 and 2

DANA	Measure	Mean		95%	t	DF	P-Val
		Group 1	Group 2	MOE			
SRT	Mean RT	343.70	322.80	38.81	1.09	40	0.2829
	Median RT	322.15	298.39	34.64	1.39	40	0.1734
	Mean RT Correct	337.52	320.89	38.27	0.88	40	0.3852
	Med RT Correct	321.48	298.29	34.66	1.35	40	0.1839
	Mean Thruput	180.57	191.52	17.94	-1.23	40	0.2243
	Median Thruput	189.10	205.55	17.87	-1.86	40	0.0703
PRT	Mean RT	611.61	617.17	57.27	-0.20	40	0.8456
	Median RT	580.74	588.08	49.46	-0.30	40	0.7658
	Mean RT Correct	610.61	615.11	55.36	-0.16	40	0.8703
	Median RT Correct	582.50	587.61	49.37	-0.21	40	0.8355
	Mean Thruput	97.90	97.63	8.69	0.06	40	0.9490
	Med Thruput	102.22	102.24	8.73	-0.00	40	0.9970
GNG	Mean RT	558.17	521.81	51.29	1.44	38	0.1593
	Med RT	526.50	490.97	50.11	1.44	38	0.1593
	Mean RT Correct	557.11	523.23	51.58	1.33	38	0.1916
	Med RT Correct	526.35	491.06	50.36	1.42	38	0.1642
	Mean Thruput	107.43	111.77	10.58	-0.83	38	0.4112
	Med Thruput	113.25	119.60	10.39	-1.24	38	0.2231

MOE is the margin of error for the difference in means, t is the test statistic, and DF is the degrees of freedom.

Table 2: Wilcoxon Rank Sum Tests for Baseline Differences Between Groups

DANA	Measure	W	P-Val	FDR P-Val
SRT	Mean RT	277.0	0.1440	0.4341
	Median RT	300.5	0.0394	0.2671
	Mean RT Correct	265.0	0.2480	0.4341
	Median RT Correct	298.5	0.0445	0.2671
	Mean Thruput	162.0	0.1586	0.4341
	Median Thruput	130.5	0.0270	0.2671
PRT	Mean RT	214.0	0.9204	1.0000
	Median RT	216.0	0.9597	1.0000
	Mean RT Correct	218.0	1.0000	1.0000
	Median RT Correct	217.5	0.9899	1.0000
	Mean Thruput	212.0	0.8808	1.0000
	Median Thruput	211.0	0.8596	1.0000
GNG	Mean RT	241.0	0.2210	0.4341
	Median RT	243.5	0.1937	0.4341
	Mean RT Correct	237.0	0.2653	0.4341
	Median RT Correct	242.0	0.2081	0.4341
	Mean Thruput	163.0	0.3855	0.5783
	Median Thruput	152.5	0.2449	0.4341

W is the test statistic, and 'FDR' indicates false discovery rate adjustment.

3.2 Post-Baseline Assessments

Part (b) of research question 1 asks whether the DANA measures on the two study groups track in parallel at each time point after baseline tests were administered. Given the magnitude of the differences in the timing of post-baseline testing between the two study groups, we caution against pooling post-baseline measures of the two groups.

Research question 2 asks whether the accumulation of physical fatigue during the night results in decrements in performance on DANA measures. Given the differences in the timing of assessments, we proceed with separate analyses of post-baseline measures for the two study groups. For group 1, we perform paired $t-$tests and Wilcoxon signed rank tests of the null hypotheses that there are no differences in baseline and post-baseline performance against the alternative that post-baseline performance is worse than at baseline (i.e., post-baseline reaction times are longer and post-baseline thruput is lower). The results of these tests confirm our conclusions from visual inspection of Figure 4. The 'Diff 1 - 0' column of Table 3 gives the mean paired difference (time 1 minus baseline) for each measure. The positive numbers in the rows for mean and median RT and RT correct indicate that reaction times after fighting were longer than at baseline. The negative numbers in the rows displaying mean and median thruput indicate that thruput was lower after fighting than at baseline. The patterns in measures of RT, RT correct, and thruput are consistent across the tests of SRT, PRT and GNG. Most of the results for SRT are significant at the $\alpha = 0.01$ level, and all are significant at the $\alpha = 0.05$ level. All tests for post-baseline differences in PRT are significant at the 0.05 level. A couple of the differences in RT for GNG are significant at the 0.05 level, and the differences in thruput for GNG are not significant. Results of the non-parametric equivalents of these tests (given in Table 4) lead to the same conclusions.

Table 3: Paired t-Tests for Differences Between Baseline and Post-Baseline Performance in Group 1

DANA	**Measure**	**Diff 1 - 0**	**95% MOE**	t	**DF**	**P-Val**	**FDR P-Val**
SRT	Mean RT	45.88	9.58	2.95	21	0.0038	0.0128
	Median RT	34.14	7.53	3.08	21	0.0029	0.0128
	Mean RT Correct	37.23	7.57	2.90	21	0.0043	0.0128
	Median RT Correct	30.68	6.47	2.98	21	0.0036	0.0128
	Mean Thruput	-21.17	5.49	-3.58	21	0.0009	0.0080
	Median Thruput	-19.86	5.30	-3.69	21	0.0007	0.0080
PRT	Mean RT	74.31	13.74	2.73	21	0.0063	0.0141
	Median RT	44.73	6.00	2.35	21	0.0143	0.0257
	Mean RT Correct	55.58	10.38	2.75	21	0.0060	0.0141
	Median RT Correct	39.25	4.81	2.28	21	0.0166	0.0272
	Mean Thruput	-8.41	1.40	-2.58	21	0.0087	0.0174
	Median Thruput	-6.67	0.74	-2.21	21	0.0192	0.0288
GNG	Mean RT	29.95	1.24	1.59	21	0.0634	0.0714
	Median RT	30.93	1.96	1.97	21	0.0311	0.0399
	Mean RT Correct	32.46	0.14	1.74	21	0.0486	0.0584
	Median RT Correct	31.48	2.64	2.07	21	0.0256	0.0354
	Mean Thruput	-3.21	2.28	-0.71	21	0.2424	0.2424
	Median Thruput	-3.48	1.95	-0.81	21	0.2129	0.2255

Table 4: Wilcoxon Signed Rank Tests for Differences Between Baseline and Post-Baseline Performance in Group 1

DANA	**Measure**	W	**P-Val**	**FDR P-Val**
SRT	Mean RT	209.0	0.0030	0.0128
	Median RT	208.0	0.0043	0.0128
	Mean RT Correct	209.0	0.0030	0.0128
	Median RT Correct	207.0	0.0037	0.0128
	Mean Thruput	34.0	0.0008	0.0075
	Median Thruput	33.0	0.0007	0.0075
PRT	Mean RT	203.0	0.0057	0.0143
	Median RT	189.0	0.0212	0.0382
	Mean RT Correct	202.0	0.0064	0.0143
	Median RT Correct	188.0	0.0238	0.0390
	Mean Thruput	62.0	0.0179	0.0359
	Median Thruput	67.0	0.0271	0.0407
GNG	Mean RT	170.0	0.0829	0.0933
	Median RT	179.0	0.0457	0.0587
	Mean RT Correct	174.0	0.0644	0.0773
	Median RT Correct	182.5	0.0358	0.0495
	Mean Thruput	93.0	0.1451	0.1451
	Median Thruput	91.0	0.1308	0.1385

For group 2, we use Friedman tests and repeated measures analysis of variance (ANOVA) to test for differences in DANA measures between *any* two time points, and follow these analyses with with pairwise paired t-tests and pairwise Wilcoxon rank sum tests for differences in DANA measures for each combination of time points (1 vs. 0, 2 vs. 0, 3 vs. 0, 2 vs. 1, 3 vs. 1, and 3 vs. 2). The ANOVA and Friedman tests for differences between the measures at any two time points (shown in Tables 5 and 6, respectively) confirm what we saw in Figure 5. Namely, there are no significant differences in any of the measures of SRT across the four assessments on group 2, and there are several significant differences in the measures of PRT and GNG across the four time points. Table 7 displays the false discovery rate-adjusted p-values of the paired t-tests and Wilcoxon rank sum tests for each combination of the time points for PRT and GNG. (Because the ANOVA and Friedman tests for SRT were not significant, no further testing was required.) Most of the p-values for the three post-baseline tests compared to baseline (columns '1 vs 0', '2 vs 0', and '3 vs 0') are significant at the $\alpha = 0.05$ level, and none of the post-baseline measures are significantly different from the measures at any other post-baseline time point. That is, tests for differences in the measures at times 2 vs. 1, 3 vs. 1, and 3 vs. 2 are not significant. Results of the pairwise comparisons for GNG are less significant but are in line with the results for PRT.

Table 5: Analysis of Variance for Differences in Performance Across Time in Group 2

DANA	Measure	$F(\mathrm{DF}_1, \mathrm{DF}_2)$	$\mathbf{DF}_1$	$\mathbf{DF}_2$	P-Val	FDR P-Val
SRT	Mean RT	1.00	3	54	0.4015	0.5162
	Median RT	0.41	3	54	0.7495	0.7533
	Mean RT Correct	1.19	3	54	0.3223	0.4576
	Median RT Correct	0.43	3	54	0.7342	0.7533
	Mean Thruput	1.17	3	54	0.3305	0.4576
	Median Thruput	0.40	3	54	0.7533	0.7533
PRT	Mean RT	5.56	3	54	0.0021	0.0102
	Median RT	5.66	3	54	0.0019	0.0102
	Mean RT Correct	5.62	3	54	0.0020	0.0102
	Median RT Correct	5.50	3	54	0.0023	0.0102
	Mean Thruput	5.18	3	54	0.0032	0.0107
	Median Thruput	4.95	3	54	0.0042	0.0107
GNG	Mean RT	4.62	3	48	0.0064	0.0144
	Median RT	2.85	3	48	0.0470	0.0845
	Mean RT Correct	3.14	3	48	0.0337	0.0674
	Median RT Correct	0.66	3	48	0.5821	0.6985
	Mean Thruput	5.04	3	48	0.0041	0.0107
	Median Thruput	1.44	3	48	0.2429	0.3975

Table 6: Friedman Tests for Differences in Performance Across Time in Group 2

DANA	Measure	χ^2	DF	P-Val	FDR P-Val
SRT	Mean RT	4.39	3	0.2224	0.2668
	Median RT	2.49	3	0.4767	0.5361
	Mean RT Correct	4.71	3	0.1947	0.2668
	Median RT Correct	2.31	3	0.5115	0.5361
	Mean Thruput	4.71	3	0.1947	0.2668
	Median Thruput	2.18	3	0.5361	0.5361
PRT	Mean RT	7.61	3	0.0548	0.1096
	Median RT	11.83	3	0.0080	0.0651
	Mean RT Correct	7.61	3	0.0548	0.1096
	Median RT Correct	11.73	3	0.0084	0.0651
	Mean Thruput	9.00	3	0.0293	0.0803
	Median Thruput	10.90	3	0.0123	0.0651
GNG	Mean RT	10.06	3	0.0181	0.0651
	Median RT	5.68	3	0.1281	0.2097
	Mean RT Correct	8.86	3	0.0312	0.0803
	Median RT Correct	5.68	3	0.1281	0.2097
	Mean Thruput	10.20	3	0.0169	0.0651
	Median Thruput	4.55	3	0.2076	0.2668

Table 7: Pairwise Paired *t*-tests and Wilcoxon Signed Rank Tests for Differences in PRT and GNG for Group 2

DANA	**Measure**	**Test**	**FDR-Adjusted P-Values**					
			1 vs 0	2 vs 0	3 vs 0	2 vs 1	3 vs 1	3 vs 2
PRT	Mean RT	t-test	0.0077	0.0077	0.0056	0.4324	0.3209	0.3209
		Wilcox	0.0280	0.1011	0.0280	0.9632	0.3410	0.1803
	Median RT	t-test	0.0197	0.0078	0.0054	0.2727	0.3723	0.5673
		Wilcox	0.1138	0.0916	0.0399	0.5171	0.4124	0.4124
	Mean RT Correct	t-test	0.0071	0.0071	0.0048	0.4258	0.2883	0.2883
		Wilcox	0.0386	0.0895	0.0278	0.9265	0.2922	0.1803
	Median RT Correct	t-test	0.0221	0.0088	0.0048	0.2968	0.3466	0.5174
		Wilcox	0.1440	0.1044	0.0399	0.5540	0.4534	0.3837
	Mean Thruput	t-test	0.0064	0.0066	0.0039	0.3366	0.2121	0.2976
		Wilcox	0.0464	0.0464	0.0278	0.9632	0.2696	0.2181
	Median Thruput	t-test	0.0180	0.0079	0.0056	0.2674	0.2674	0.4759
		Wilcox	0.1428	0.0800	0.0474	0.6441	0.4534	0.3652
GNG	Mean RT	t-test	0.0008	0.0514	0.0293	0.7282	0.2387	0.0514
		Wilcox	0.0101	0.0610	0.0610	0.4845	0.5791	0.3370
	Median RT	t-test	0.0584	0.0584	0.0584	0.2693	0.1150	0.0584
		Wilcox	0.1766	0.1766	0.1766	0.8128	0.4591	0.4885
	Mean RT Correct	t-test	0.0022	0.1487	0.0726	0.7581	0.3106	0.0726
		Wilcox	0.0101	0.0697	0.1011	0.5168	0.6441	0.3652
	Median RT Correct	t-test	0.1478	0.3372	0.3372	0.4946	0.3805	0.3152
		Wilcox	0.2595	0.2595	0.2595	0.8129	0.4591	0.6084
	Mean Thruput	t-test	0.0008	0.0525	0.0210	0.8061	0.1918	0.0525
		Wilcox	0.0039	0.0330	0.0464	0.3160	0.5477	0.2851
	Median Thruput	t-test	0.0831	0.2865	0.1607	0.5468	0.2559	0.0831
		Wilcox	0.2142	0.2404	0.2142	0.7819	0.4534	0.4262

A Supplemental Tables

Table 8: Summary Statistics for Group 1

DANA	Measure	Time	n	Min	Q_1	Median	Mean	SD	Q_3	Max
SRT	Mean RT	0	23	261.60	300.50	326.60	343.70	63.49	366.80	541.00
		1	22	281.50	344.50	388.50	392.30	69.15	435.30	513.70
	Median RT	0	23	256.50	284.00	302.00	322.20	56.23	348.20	493.00
		1	22	265.00	312.60	361.80	358.30	56.77	395.90	467.00
	Mean RT Correct	0	23	261.60	295.50	325.30	337.50	62.51	364.60	541.00
		1	22	281.50	330.20	382.00	377.20	57.47	411.40	470.80
	Median RT Correct	0	23	256.50	283.00	302.00	321.50	56.23	348.00	493.00
		1	22	265.00	312.60	353.00	354.20	53.10	393.80	440.50
	Mean Thruput	0	23	110.90	164.60	183.70	180.60	27.97	199.70	229.40
		1	22	114.70	138.10	155.10	158.00	29.16	177.20	213.10
	Median Thruput	0	23	121.70	170.40	189.60	189.10	28.00	211.30	233.90
		1	22	122.60	145.70	165.40	168.00	29.93	190.70	226.40
PRT	Mean RT	0	23	471.70	539.30	613.80	611.60	89.74	655.80	782.40
		1	22	416.20	582.00	714.70	690.50	132.41	771.10	981.80
	Median RT	0	23	453.50	527.00	584.50	580.70	73.00	627.80	723.00
		1	22	399.00	558.90	648.80	629.10	100.56	700.60	855.50
	Mean RT Correct	0	23	469.10	541.00	610.30	610.60	87.82	656.10	787.10
		1	22	418.90	583.10	677.00	670.70	109.54	760.60	836.40
	Median RT Correct	0	23	448.00	535.80	584.50	582.50	73.21	634.20	713.00
		1	22	399.00	558.50	640.50	625.50	97.59	698.10	817.50
	Mean Thruput	0	23	73.85	89.83	96.56	97.90	14.05	107.50	123.90
		1	22	62.77	75.64	85.68	88.78	16.37	100.90	134.30
	Median Thruput	0	23	80.36	92.69	102.60	102.20	13.39	110.20	129.70
		1	22	64.22	83.26	91.57	94.90	16.41	105.60	141.00
GNG	Mean RT	0	23	394.70	511.10	533.50	558.20	83.06	608.90	770.10
		1	22	405.10	510.10	558.90	589.60	120.80	656.10	913.30
	Median RT	0	23	388.00	491.50	510.00	526.50	73.58	552.20	749.00
		1	22	396.00	471.20	536.00	559.40	108.67	615.20	840.00
	Mean RT Correct	0	23	394.70	511.10	533.50	557.10	85.35	608.90	770.10
		1	22	405.10	510.10	558.90	591.00	121.61	665.50	913.30
	Median RT Correct	0	23	388.00	491.50	510.00	526.30	74.38	556.00	749.00
		1	22	396.00	471.20	536.00	559.80	108.86	621.20	840.00
	Mean Thruput	0	23	77.92	95.84	111.90	107.40	16.50	116.60	152.00
		1	22	65.69	88.89	105.60	103.90	20.07	117.70	148.10
	Median Thruput	0	23	80.11	101.70	116.70	113.20	15.50	121.30	154.60
		1	22	71.43	93.94	110.60	109.30	19.78	124.60	151.50

Table 9: Summary Statistics for Group 2

DANA	Measure	Time	n	Min	Q_1	Median	Mean	SD	Q_3	Max
SRT	Mean RT	0	19	251.50	280.80	309.10	322.80	60.00	340.70	486.70
		1	19	235.60	265.50	294.20	304.80	50.42	330.70	428.80
		2	19	268.20	283.40	295.80	338.20	102.46	328.50	620.80
		3	19	244.70	286.40	309.00	323.20	67.13	339.60	564.00
	Median RT	0	19	243.50	266.80	282.50	298.40	54.10	308.50	459.00
		1	19	237.00	254.50	278.50	286.40	36.34	319.20	349.50
		2	19	240.50	266.50	281.00	297.50	54.71	322.80	470.00
		3	19	234.50	276.20	293.00	295.50	29.82	311.50	364.00
	Mean RT Correct	0	19	251.50	280.80	309.10	320.90	59.28	335.30	486.70
		1	19	239.10	268.10	294.20	301.10	41.15	330.70	393.90
		2	19	268.20	283.50	302.90	333.20	86.36	328.50	560.10
		3	19	244.70	286.40	309.00	321.70	60.17	339.60	527.20
	Median RT Correct	0	19	243.50	266.20	282.50	298.30	54.17	308.50	459.00
		1	19	237.00	255.00	278.50	286.20	35.71	319.20	348.00
		2	19	241.00	266.50	281.00	295.90	49.72	322.80	441.50
		3	19	234.50	276.20	293.00	295.30	29.22	311.50	359.00
	Mean Thruput	0	19	123.30	179.00	194.10	191.50	29.41	213.70	238.60
		1	19	152.30	181.40	203.90	201.30	26.10	221.00	244.70
		2	19	104.00	182.60	197.00	187.50	35.61	210.30	223.80
		3	19	111.00	176.70	194.10	191.00	29.15	209.50	245.20
	Median Thruput	0	19	130.70	194.60	212.40	205.50	29.15	222.90	246.40
		1	19	165.90	188.00	215.40	211.30	25.50	233.00	246.80
		2	19	129.10	185.90	210.40	206.30	30.68	225.10	247.90
		3	19	163.00	191.10	204.80	204.60	21.01	217.20	255.90
PRT	Mean RT	0	19	508.70	538.50	604.90	617.20	93.40	689.40	802.90
		1	19	470.90	522.10	568.30	568.40	65.18	620.90	710.80
		2	19	430.30	502.10	561.60	565.90	70.84	617.40	687.00
		3	19	404.30	514.50	553.50	555.20	76.02	594.10	716.30
	Median RT	0	19	488.50	513.50	569.50	588.10	85.64	654.50	738.50
		1	19	459.00	493.00	517.00	544.10	61.25	593.80	656.50
		2	19	426.00	487.20	537.00	533.40	57.51	584.20	632.00
		3	19	390.00	498.00	537.50	535.70	68.28	555.80	672.00
	Mean RT Correct	0	19	510.60	538.90	603.30	615.10	89.00	691.60	790.60
		1	19	477.00	522.70	551.90	568.00	64.47	620.90	710.80
		2	19	430.30	502.10	563.30	565.20	70.34	613.20	689.70
		3	19	404.80	515.70	551.20	553.20	72.21	590.20	685.80
	Median RT Correct	0	19	488.50	511.80	569.50	587.60	85.12	656.00	734.00
		1	19	467.00	490.20	517.00	544.40	60.81	593.80	656.50
		2	19	426.00	490.00	537.00	534.30	57.69	580.00	632.00
		3	19	389.00	495.00	537.50	534.90	68.10	552.00	670.00
	Mean Thruput	0	19	73.53	85.39	97.71	97.63	13.63	108.80	116.30
		1	19	84.41	96.65	104.90	105.10	11.46	113.30	122.20
		2	19	84.27	96.32	103.20	106.50	14.81	119.50	139.40
		3	19	79.29	99.75	108.00	108.70	15.26	114.50	143.60
	Median Thruput	0	19	79.19	90.03	105.40	102.20	14.56	114.50	122.80
		1	19	88.93	99.72	114.70	109.60	11.57	118.80	124.20
		2	19	93.60	102.10	110.90	112.20	13.27	122.40	140.80
		3	19	81.16	104.80	111.60	112.30	15.33	119.40	149.40

continued on next page...

Table 9: Summary Statistics for Group 2 (continued from previous page)

DANA	Measure	Time	n	Min	Q_1	Median	Mean	SD	Q_3	Max
GNG	Mean RT	0	17	370.60	466.00	541.90	521.80	73.57	570.70	654.50
		1	18	356.30	442.70	490.10	489.30	70.61	528.00	637.40
		2	19	417.90	458.40	495.70	506.60	63.80	542.90	676.50
		3	19	395.30	442.30	480.20	480.30	53.84	495.90	599.00
	Median RT	0	17	309.50	435.00	465.00	491.00	82.33	557.00	626.00
		1	18	314.50	432.50	483.00	479.00	73.09	526.80	630.00
		2	19	366.50	438.80	465.00	480.50	61.83	520.00	626.00
		3	19	397.00	425.50	460.00	462.30	45.81	487.00	579.00
	Mean RT Correct	0	17	389.10	466.00	541.90	523.20	71.09	570.70	654.50
		1	18	404.30	442.70	490.10	493.00	65.76	529.60	637.40
		2	19	417.90	458.40	509.10	511.90	65.94	556.60	676.50
		3	19	395.30	442.30	482.10	486.10	57.30	510.40	599.00
	Median RT Correct	0	17	310.00	435.00	465.00	491.10	82.23	557.00	626.00
		1	18	326.00	432.50	483.00	480.80	71.96	526.80	630.00
		2	19	416.00	442.00	483.00	488.20	55.62	520.00	626.00
		3	19	397.00	439.00	464.00	473.30	55.91	493.50	618.00
	Mean Thruput	0	17	77.09	103.00	110.60	111.80	16.11	124.90	136.90
		1	18	72.83	109.40	120.50	119.30	19.35	135.10	148.40
		2	19	47.96	106.00	117.90	115.50	21.73	130.00	143.60
		3	19	52.69	116.80	124.40	122.00	21.67	135.70	151.80
	Median Thruput	0	17	95.85	104.40	119.80	119.60	16.76	136.00	143.20
		1	18	92.02	112.00	121.20	122.10	17.20	137.70	149.60
		2	19	54.96	112.50	124.20	120.40	20.89	133.80	144.20
		3	19	48.54	121.60	128.20	125.50	22.00	136.80	151.10

Appendix S

MEMORANDUM

To: Cori Lathan, Lawrence Wolpert
From: Helaine Resnick
Re: Air Force Data Distributions and Critical Values
Date: September 3, 2013

This memo summarizes my impressions concerning the distributions of the "Air Force" DANA data and how these distributions may relate to future efforts aimed at identifying threshold values that can be used for screening and triage.

The Air Force data set contained information for SRT, PRT and GNG testing that was conducted at three points in time over the course of approximately 8 months. We examined each of the three tests at each of the three points in time. We also examined both means and median values for each test as well as both throughput and "pre-throughput" values.

The attached PDFs files are sorted according to each test, with one PDF for each test. These files show smoothed curves superimposed over histograms of the raw data as I received them. Each panel also contains descriptive statistics, including the sample size on which the curve is based, as well as quartiles, means and standard deviations.

Using the mean and standard deviation from each curve, we calculated critical values at the first, second and third standard deviations above the mean for each distribution. These values can provide an initial glimpse about how these data (when examined together or pooled with similar information from other DANA protocols) could be used in the future to define thresholds above which an individual's cognitive function could be defined as "out of normal range."

Over the course of the Air Force data study, the sample size diminished as time passed. The initial data collection included approximately 142 individuals, of whom 96 were examined at the second point in time, and only approximately 58 providing data at the third time point. Across all tests (e.g. SRT, PRT and GNG) the impact of diminishing sample size on the shape of the curves is evident. The curves are wider and smoother when the sample sizes are larger and tall and choppy as sample size diminishes.

In general, it does not appear that the shapes of the curves are influenced to a high degree by whether mean or median values are used. For the "pre-throughput" data (blue shaded data on the spreadsheet), mean values are slightly higher than median values, but the shapes of the curves are similar. Since threshold values that are used for clinical purposes depend on means and standard deviations from the raw data, the Air Force data suggest that if the "pre-throughput" data are used for this purpose, mean values will be slightly less likely to define someone as "out of range" because these values are slightly higher than medians. The throughput data appear to show the opposite pattern: Median values are higher than mean values. Thus, for the Air Force data, if clinical thresholds are based on throughput values, use of medians would likely result in fewer people being tagged as out of range because the medians are higher than the means.

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It is important to stress that the range of values for the pre-throughput vs. throughput data are quite different. The range of throughput values is substantially smaller than the pre-throughput values. Importantly, the shape of the curves that are derived using throughput data are more symmetric than those for pre-throughout values. That is, the throughput data tend to generate curves whose upper and lower tails are more pronounced, while the mean values tend to generate curves with very pronounced upper tails and a blunted or absent lower tail. It is possible that the symmetric nature of the throughput data may make them more favorable for use in defining threshold values because the means of the throughput data will be better centered in the curves.

The attached spreadsheet contains a summary of the sample sizes for each test and time point, as well as means, standard deviations and critical values at the first, second and third standard deviation above the mean for the various types of data that were examined. As noted above, the pre-throughput data are in blue, and the throughput data are in gray.

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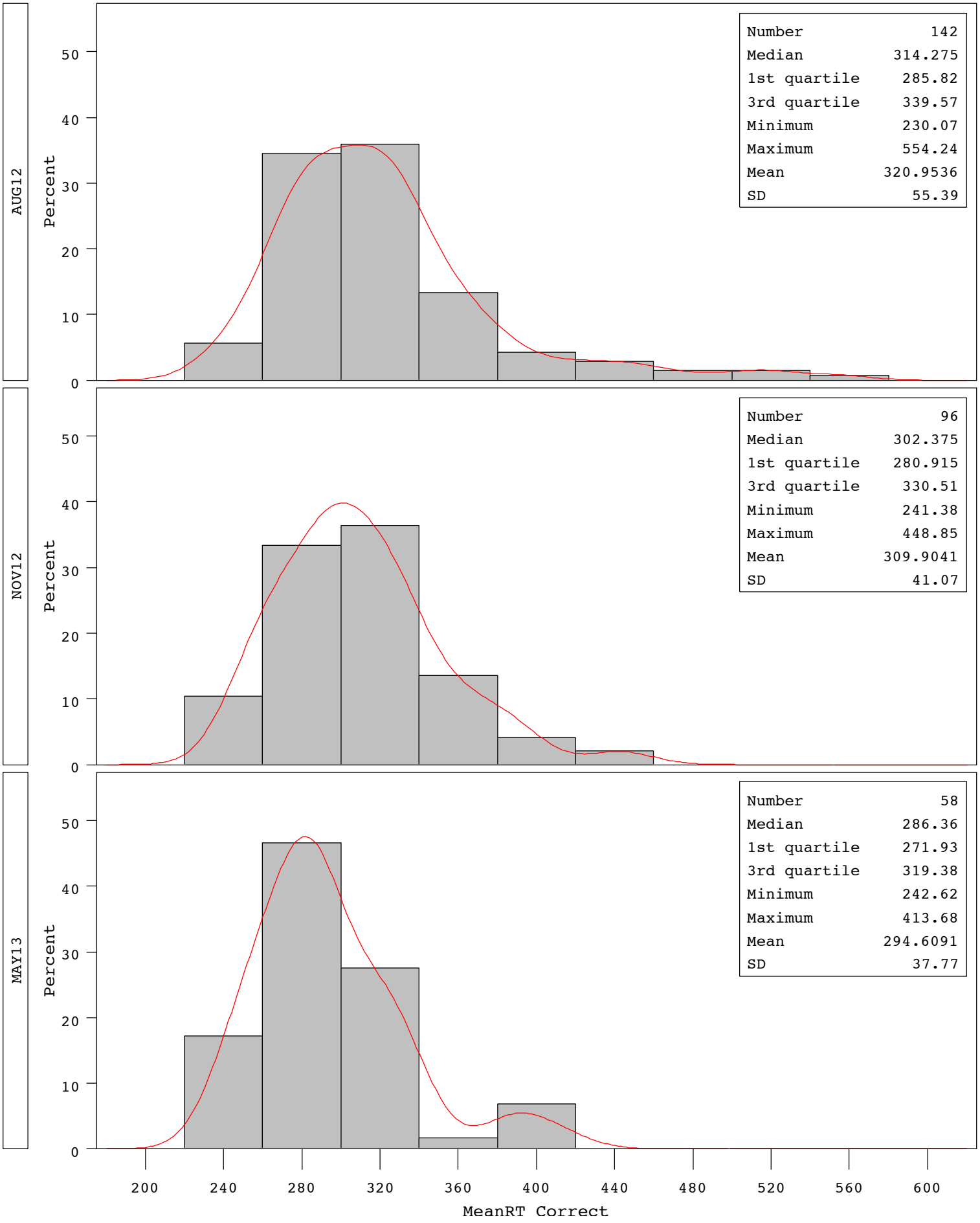
SRT: Mean RT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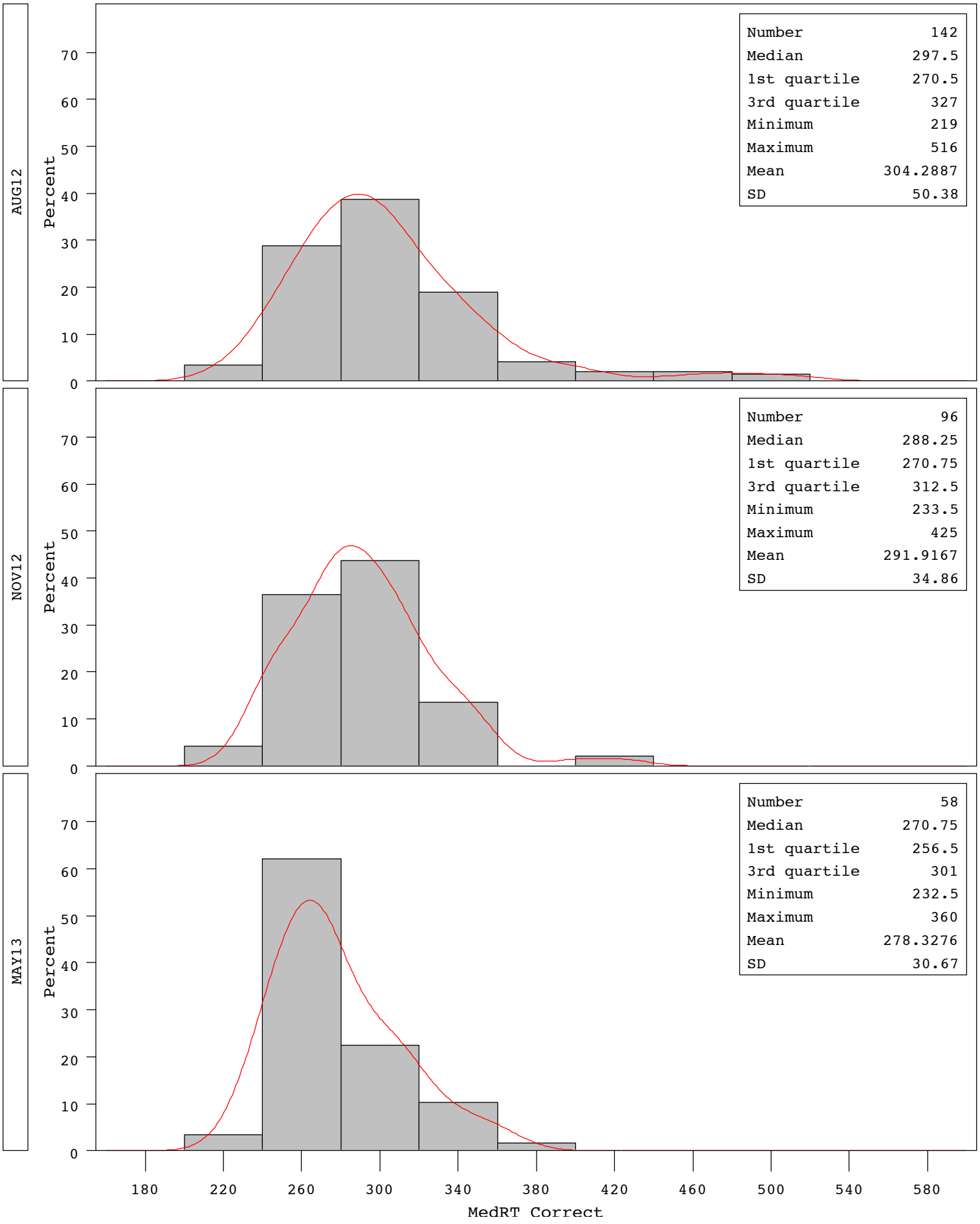
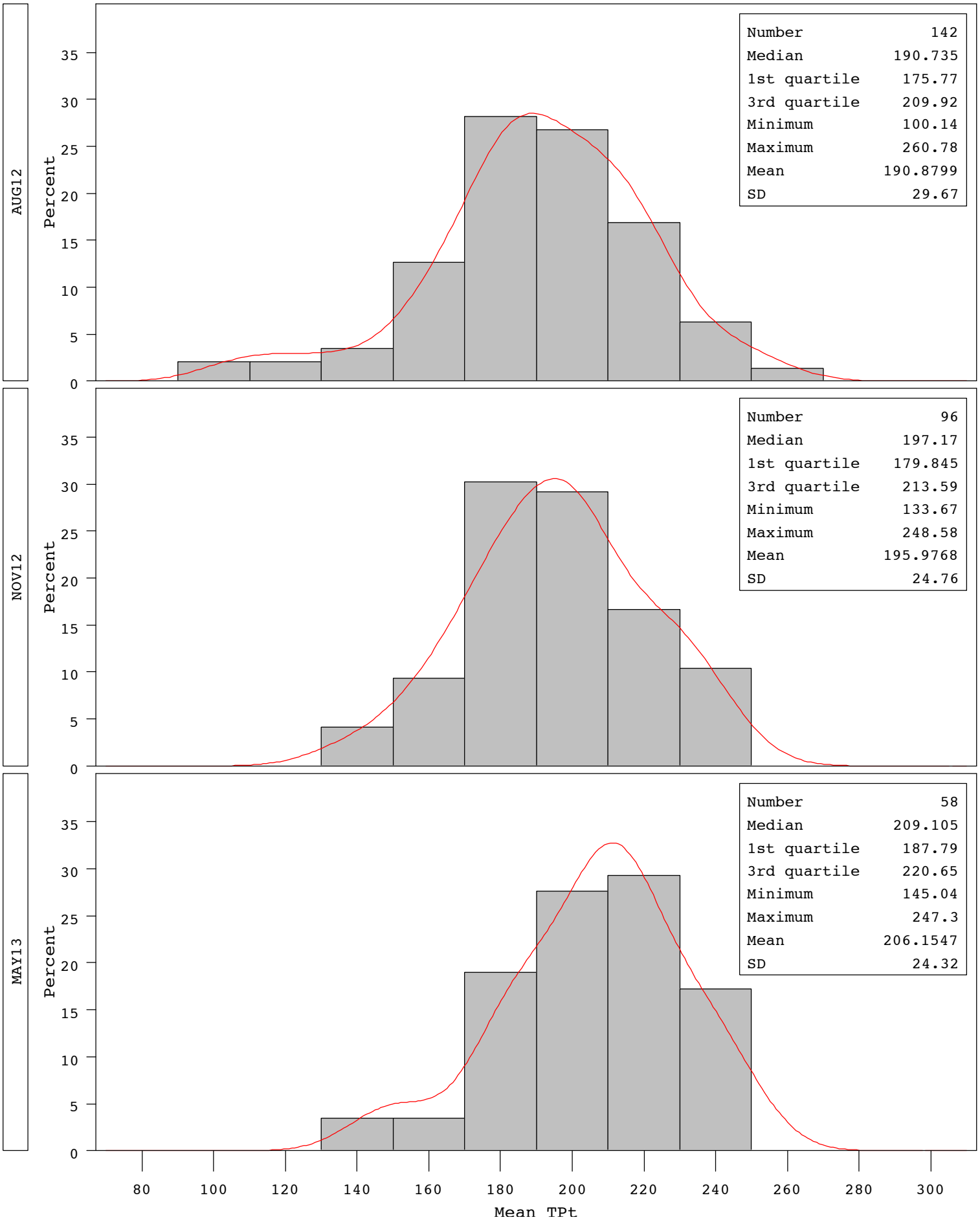
Percent
Number 142
Median 314.275
1st quartile 285.82
3rd quartile 339.57
Minimum 230.07
Maximum 554.24
Mean 320.9536
SD 55.39
NOV12
Percent
Number 96
Median 302.375
1st quartile 280.915
3rd quartile 330.51
Minimum 241.38
Maximum 448.85
Mean 309.9041
SD 41.07
MAY13
Percent
Number 58
Median 286.36
1st quartile 271.93
3rd quartile 319.38
Minimum 242.62
Maximum 413.68
Mean 294.6091
SD 37.77
0 10 20 30 40 50
200 240 280 320 360 400 440 480 520 560 600
MeanRT Correct

SRT: Median RT



SRT: Mean TPT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Percent
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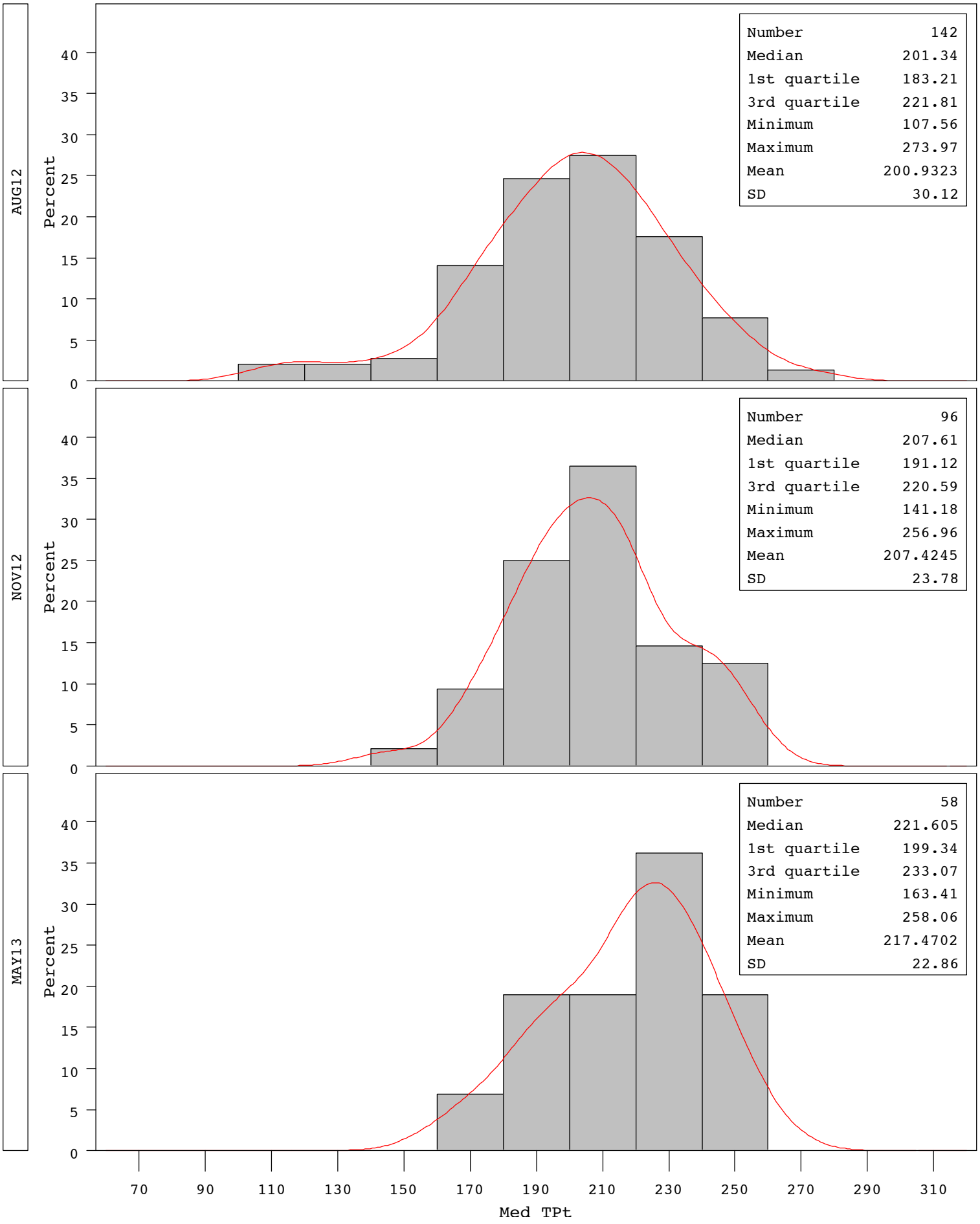
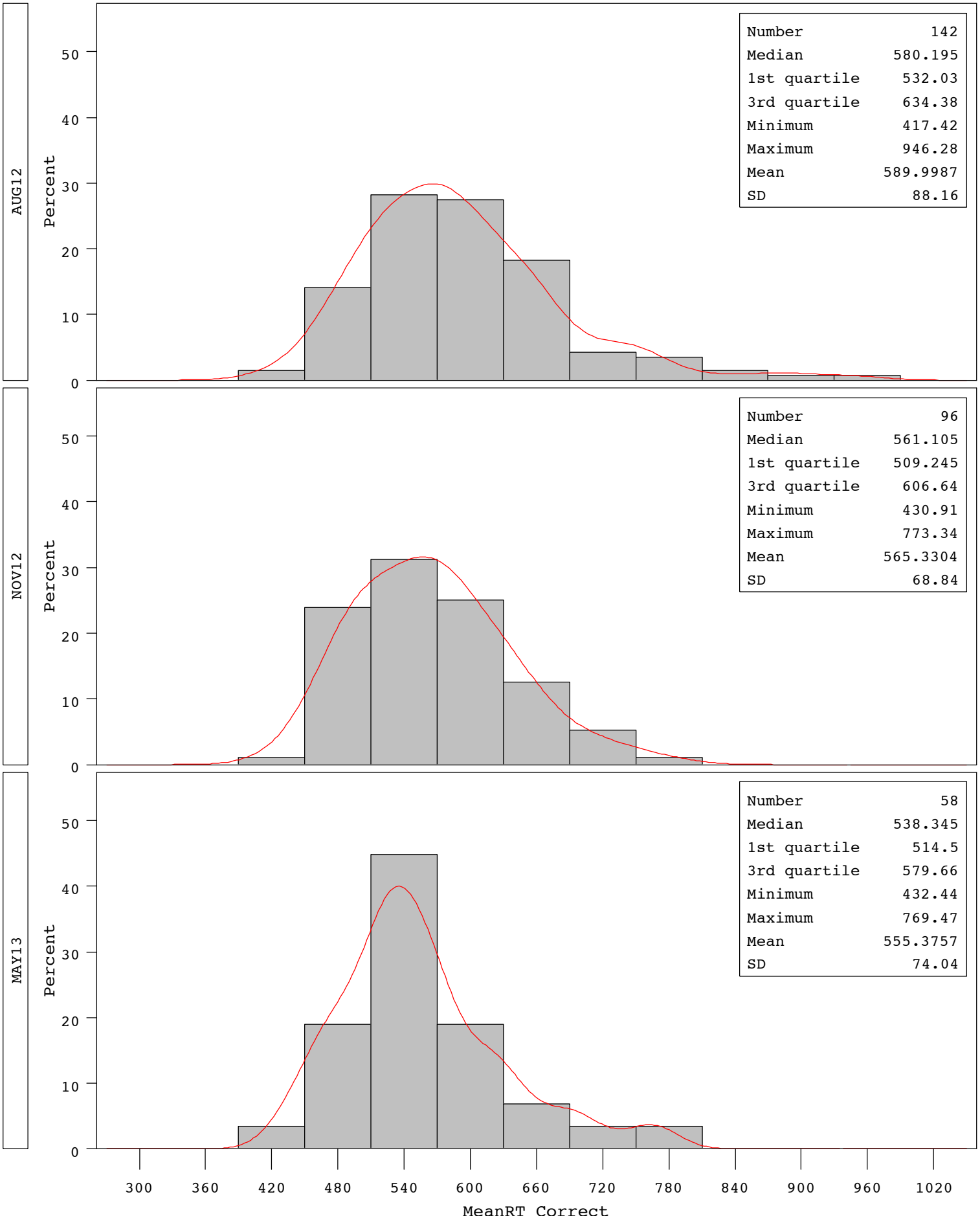
3rd quartile 209.92
Minimum 100.14
Maximum 260.78
Mean 190.8799
SD 29.67
NOV12
Percent
Number 96
Median 197.17
1st quartile 179.845
3rd quartile 213.59
Minimum 133.67
Maximum 248.58
Mean 195.9768
SD 24.76
MAY13
Percent
Number 58
Median 209.105
1st quartile 187.79
3rd quartile 220.65
Minimum 145.04
Maximum 247.3
Mean 206.1547
SD 24.32
0 5 10 15 20 25 30 35
80 100 120 140 160 180 200 220 240 260 280 300
Mean TPt

SRT: Median TPT



PRT: Mean RT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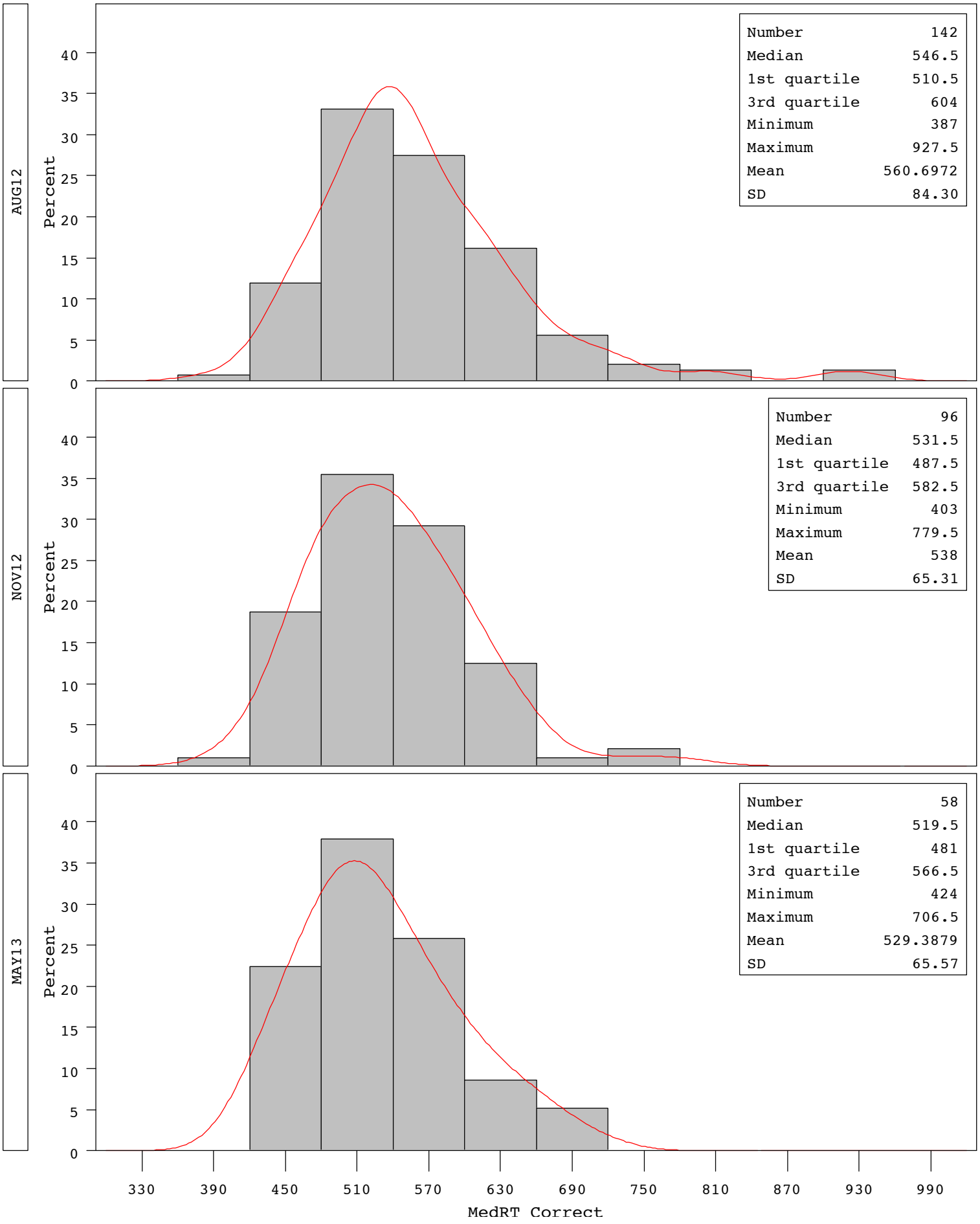
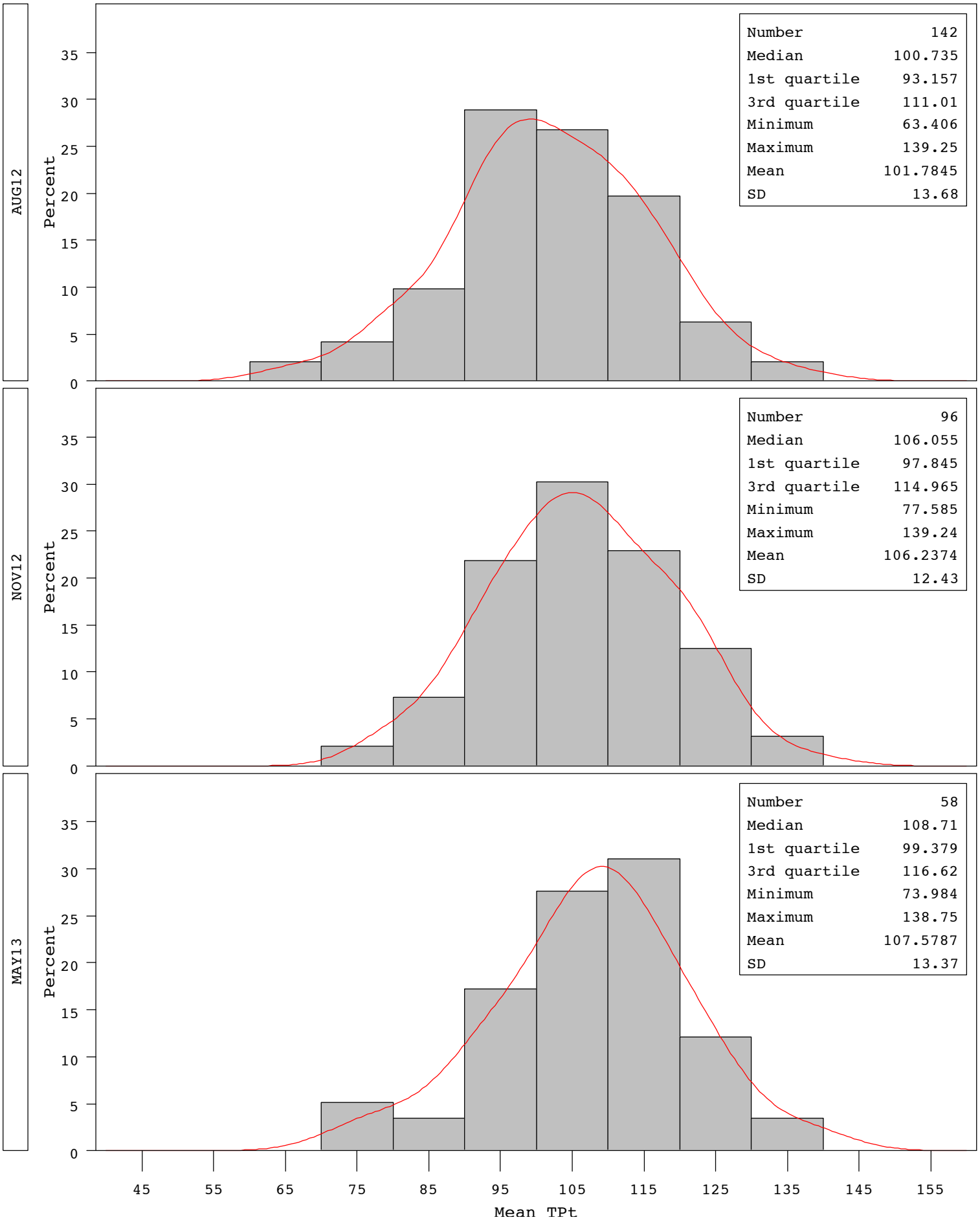
Maximum 946.28
Mean 589.9987
SD 88.16
NOV12
Percent
Number 96
Median 561.105
1st quartile 509.245
3rd quartile 606.64
Minimum 430.91
Maximum 773.34
Mean 565.3304
SD 68.84
MAY13
Percent
Number 58
Median 538.345
1st quartile 514.5
3rd quartile 579.66
Minimum 432.44
Maximum 769.47
Mean 555.3757
SD 74.04
0
10
20
30
40
50
300
360
420
480
540
600
660
720
780
840
900
960
1020
MeanRT Correct

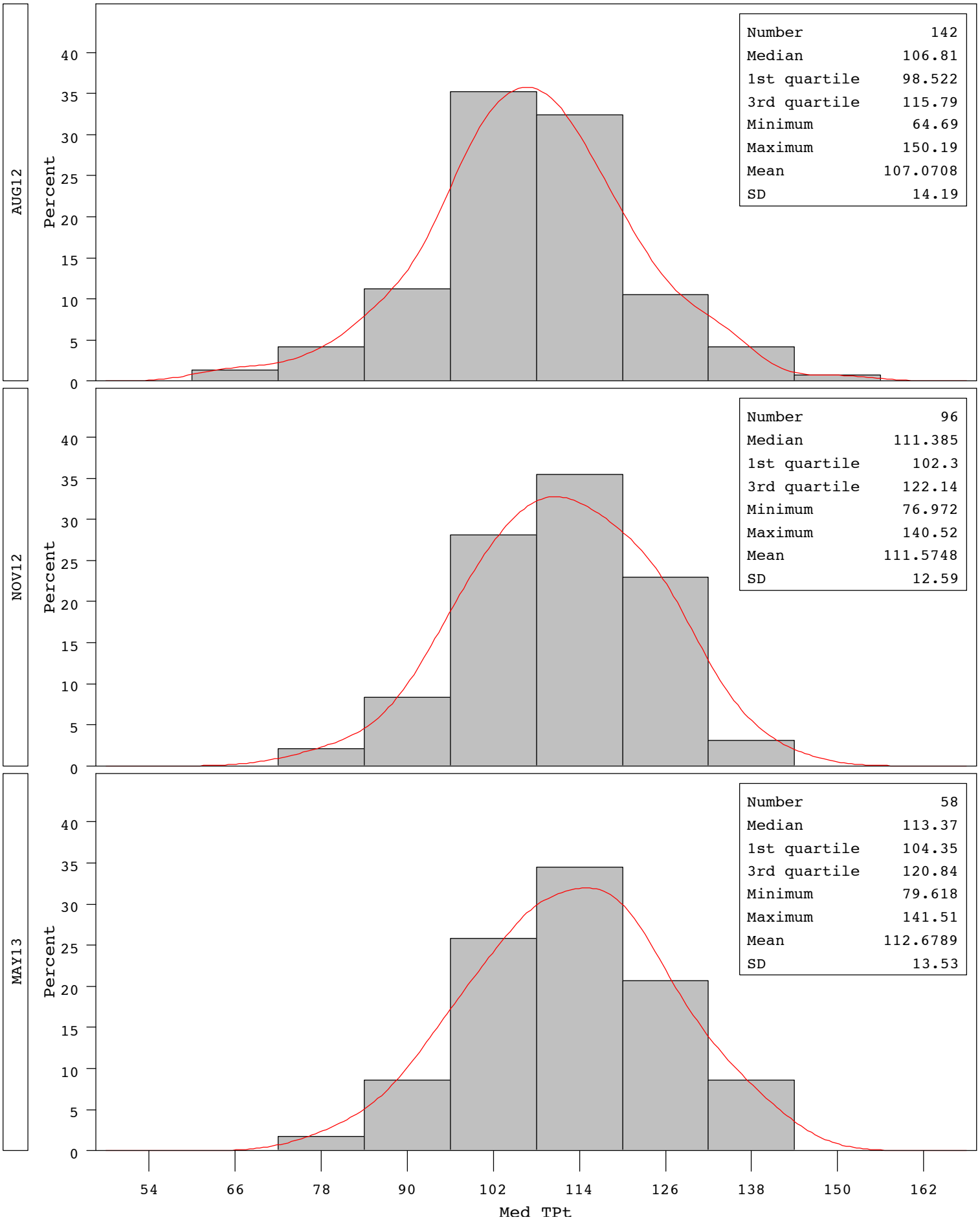
PRT: Median RT



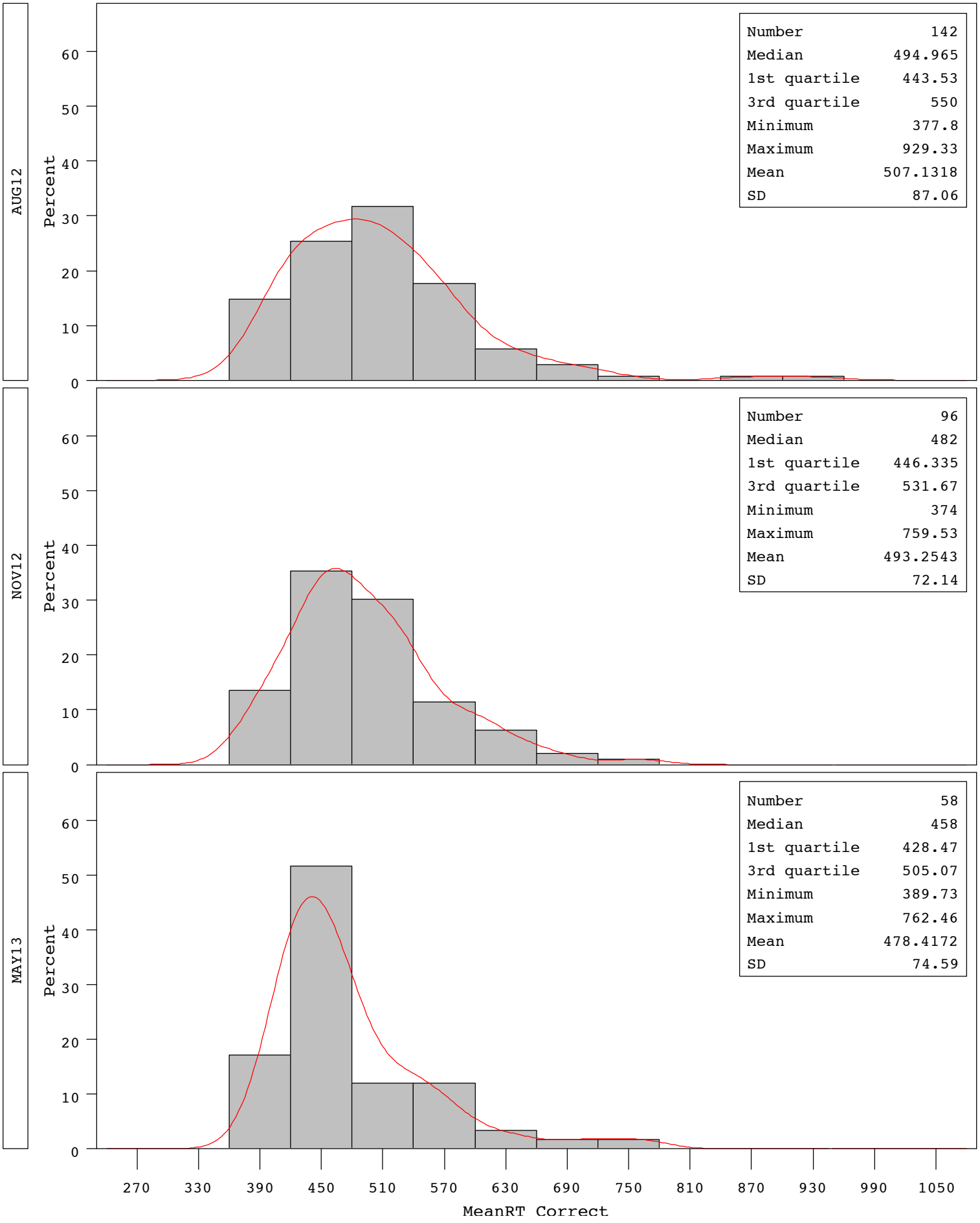
PRT: Mean TPT


AUG12
Percent
Number 142
Median 100.735
1st quartile 93.157
3rd quartile 111.01
Minimum 63.406
Maximum 139.25
Mean 101.7845
SD 13.68
NOV12
Percent
Number 96
Median 106.055
1st quartile 97.845
3rd quartile 114.965
Minimum 77.585
Maximum 139.24
Mean 106.2374
SD 12.43
MAY13
Percent
Number 58
Median 108.71
1st quartile 99.379
3rd quartile 116.62
Minimum 73.984
Maximum 138.75
Mean 107.5787
SD 13.37
0 5 10 15 20 25 30 35
45 55 65 75 85 95 105 115 125 135 145 155
Mean TPt

PRT: Median TPT



GNG: Mean RT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Percent
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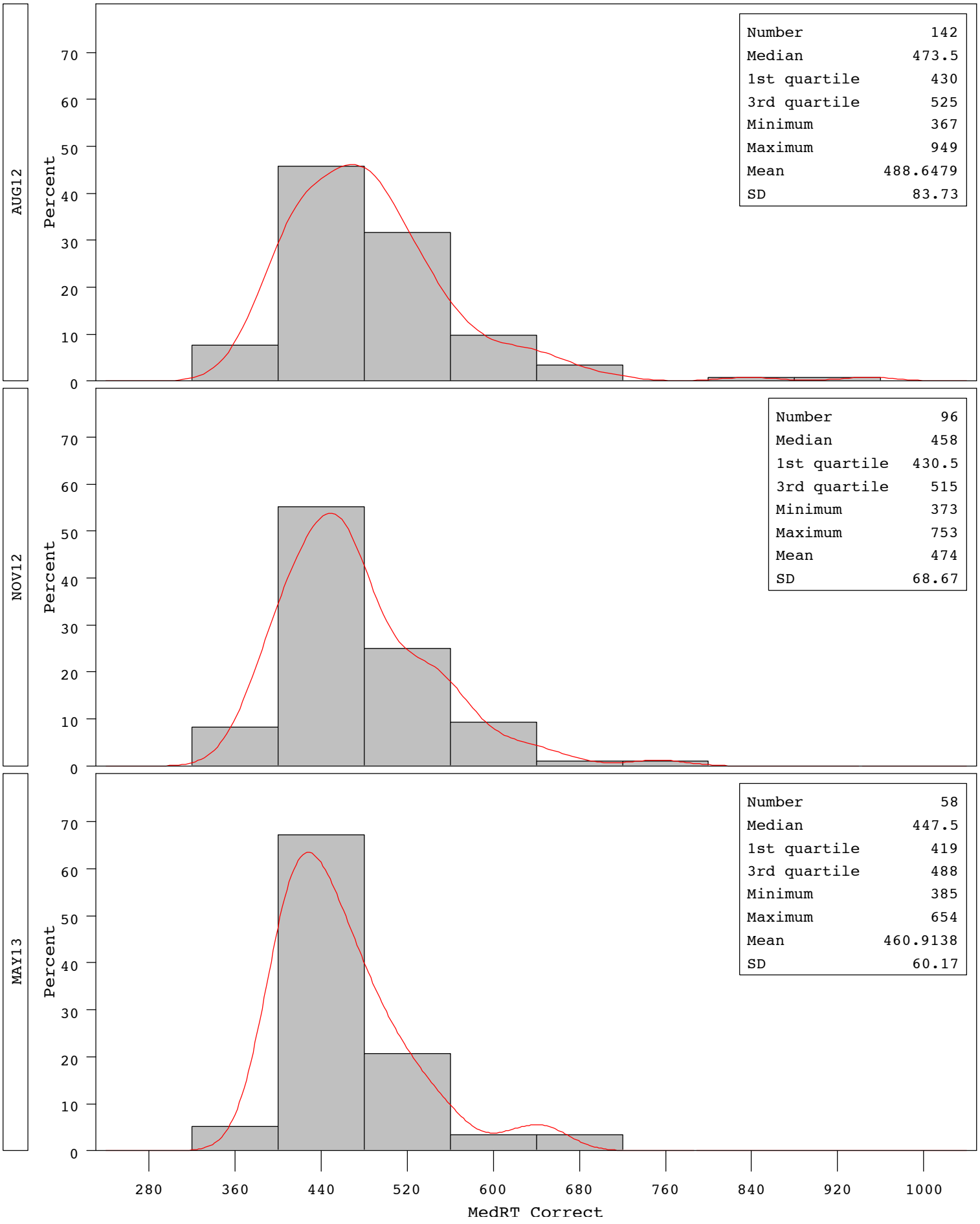
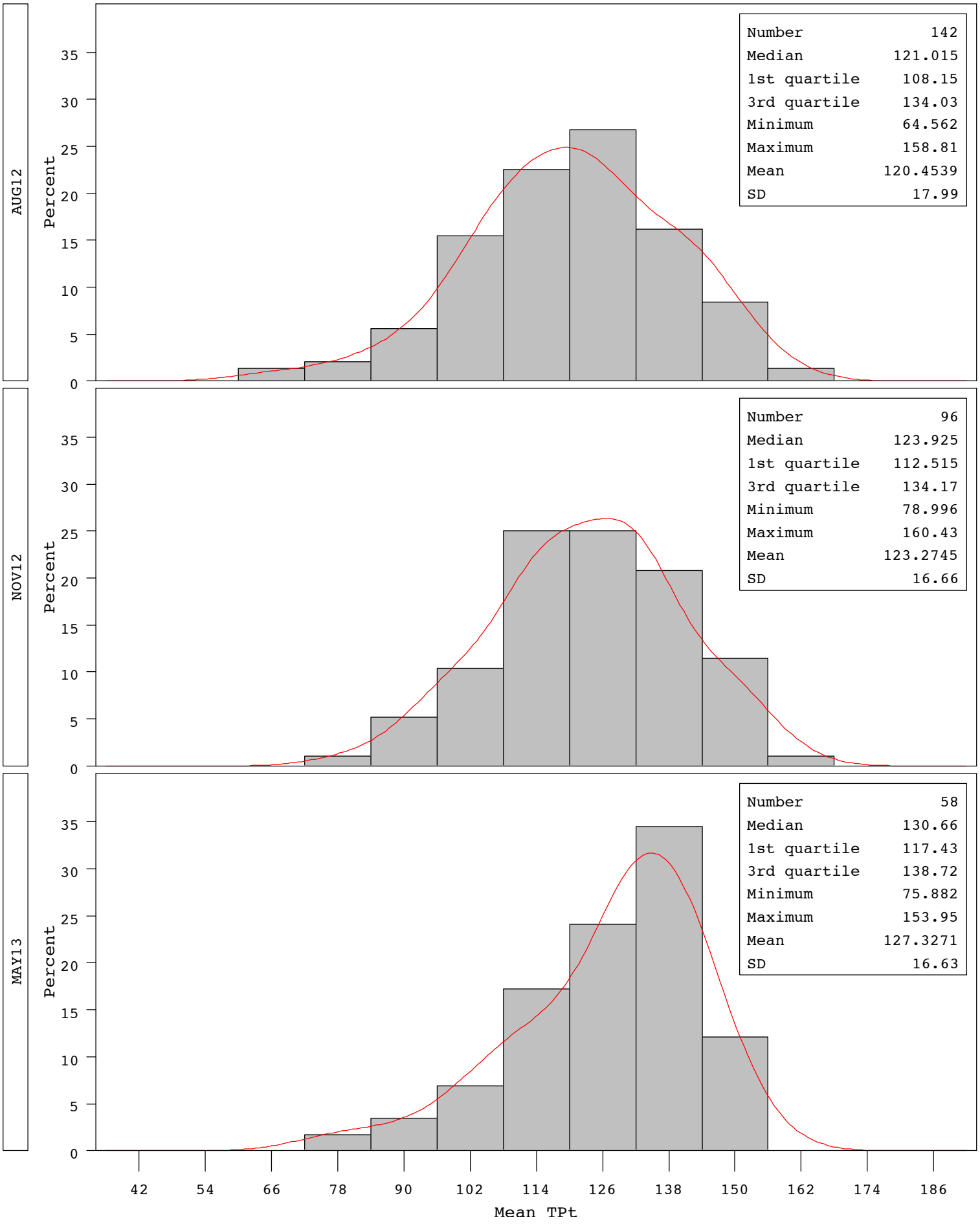
3rd quartile 550
Minimum 377.8
Maximum 929.33
Mean 507.1318
SD 87.06
NOV12
Percent
Number 96
Median 482
1st quartile 446.335
3rd quartile 531.67
Minimum 374
Maximum 759.53
Mean 493.2543
SD 72.14
MAY13
Percent
Number 58
Median 458
1st quartile 428.47
3rd quartile 505.07
Minimum 389.73
Maximum 762.46
Mean 478.4172
SD 74.59
0
10
20
30
40
50
60
270
330
390
450
510
570
630
690
750
810
870
930
990
1050
MeanRT Correct

GNG: Median RT



GNG: Mean TPT


AUG12
Percent
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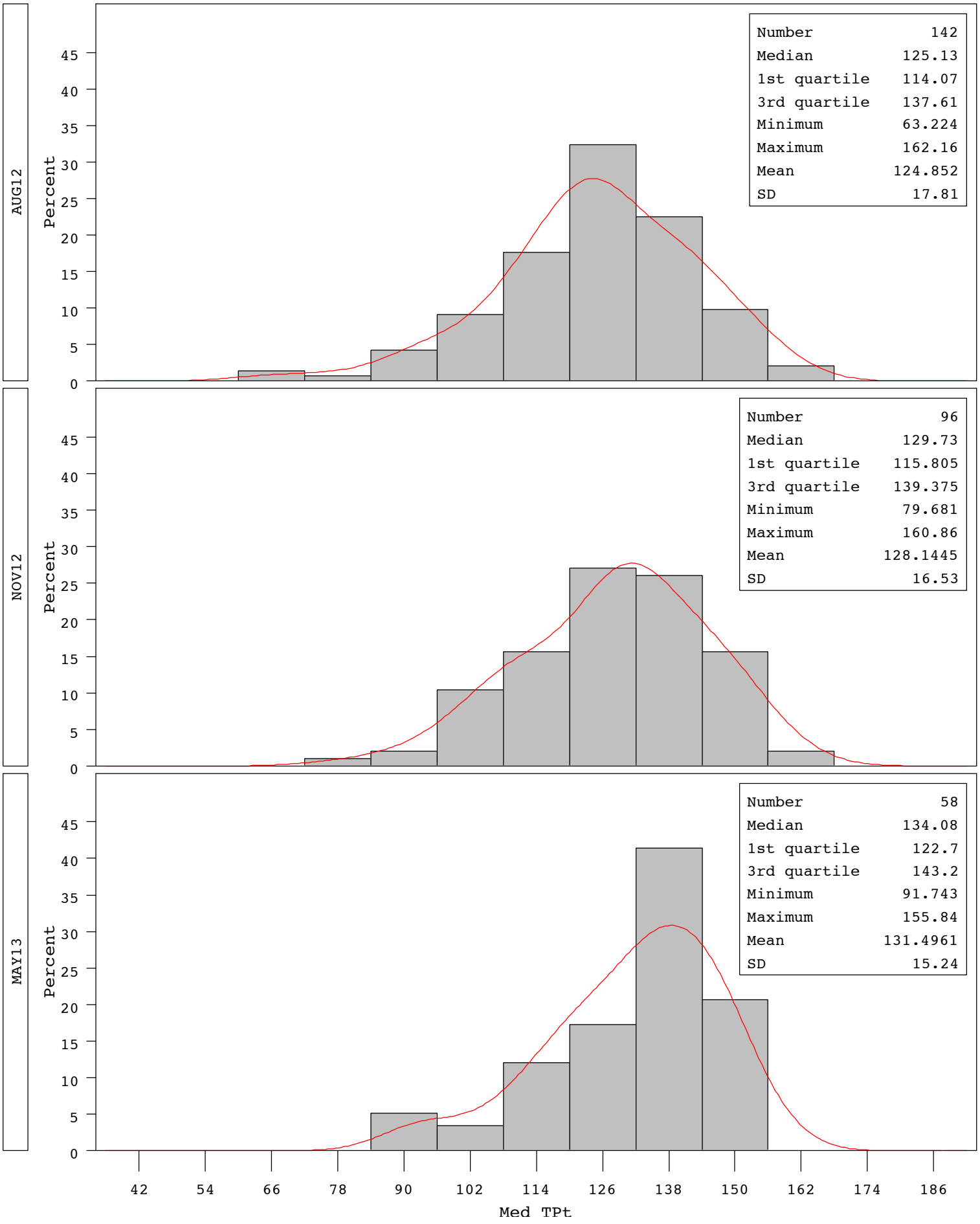
1st quartile 108.15
3rd quartile 134.03
Minimum 64.562
Maximum 158.81
Mean 120.4539
SD 17.99
NOV12
Percent
Number 96
Median 123.925
1st quartile 112.515
3rd quartile 134.17
Minimum 78.996
Maximum 160.43
Mean 123.2745
SD 16.66
MAY13
Percent
Number 58
Median 130.66
1st quartile 117.43
3rd quartile 138.72
Minimum 75.882
Maximum 153.95
Mean 127.3271
SD 16.63
0 5 10 15 20 25 30 35
42 54 66 78 90 102 114 126 138 150 162 174 186
Mean TPt

GNG: Median TPT



Appendix T

A Comparison of Defense Automated Neurobehavioral Assessments and Automated Neuropsychological Assessment Metrics

Prepared by: Resnick, Chodorow, and Associates

September 18, 2014

Contents

List of Figures

List of Tables

1 Overview

The data are summaries of paired repeated measures of Defense Automated Neurobehavioral Assessments (DANA) and Automated Neuropsychological Assessment Metrics (ANAM). Each assessment is comprised of four tests: code substitution delayed (CSD), code substitution learning (CSL), simple reaction time (SRT), and procedural reaction time (PRT). The results of each assessment include mean reaction time (RT) and mean thruput. The objective of this analysis is to understand how DANA measures differ from ANAM measures on similar tests. The two testing schemes use different platforms/devices and this is thought to result in a systematic measurement difference in RT of about 50 milliseconds between the two devices. This analysis explores differences in thruput as measured by the two devices, and investigates the hypothesis that there is a fifty millisecond difference between DANA-measured and ANAM-measured reaction times.

2 Data

We begin with a description of the data used in this analysis. Table 1 lists the names of each of the six data sets along with the provided description of each data source.

Table 1: Description of Data Sources

File Name	**Provided Description**
DANAvANAM_DANA_Controls.csv	SRT, PRT, CSD and CSL measured by DANA on 17 non-injured subjects
DANAvANAM_ANAM_Controls.csv	SRT, PRT, CSD and CSL measured by ANAM on the same 17 non-injured subjects in the DANA controls file
DANAvANAM_Flagged_DANA.csv	Information on DANA administrations that did not pass quality control standards (to be excluded from analysis)
ANAM_data(2) (2).xls	Subject IDs and injury dates for injured individuals (should not be found in controls data)
Email from Dr. Resnick on 9/10/14	List of subjects with concussions (should not be found in controls data)
ANAM_DANA_subjects_key.csv	Linking file to merge injury data with controls data

Upon inspection of the various data sources, we found:

- twenty-three subjects in the ANAM controls,
- twenty-two subjects in the DANA controls,
- two subjects in the injuries file (ANAM_data(2) (2).xls) who are not in the key file (ANAM_DANA_subjects_key.csv) and therefore can not be linked to the controls data,
- two subjects in the list of individuals with concussions who are not in the injuries file, and
- one subject with ANAM test dates in 2013 and DANA test dates in 1970.

After excluding individuals found in either the injuries file or the concussion list, we are left with eighteen non-injured subjects who have at least one valid set of both DANA and ANAM tests. For a count of subjects by test and assessment number, please see Tables 3 and 4 in the appendix.

3 Results

Figure 1 displays the paired differences between mean DANA-measured and ANAM-measured reaction time and thruput by test and time (assessment number). In each of the eight sub-figures, time is shown on the x-axis and the paired difference (DANA - ANAM) in milliseconds is shown on the y-axis. In the plot of paired differences for SRT (upper left sub-figure), the distributions of the difference in mean reaction times are roughly symmetric around fifty milliseconds for assessments 1, 2, 3, 4, and 6, and roughly symmetric around seventy-five for assessment 5. The plot of differences in mean reaction times in tests of PRT (column 1, row 2) also reveals distributions that are roughly symmetric around fifty milliseconds for each of the three paired assessments. Tests of CSD (column 1, row 3) show similar differences in mean reaction times in assessments 1 and 3, and greater variability in the paired differences from assessment 2. Tests of CSL (bottom left sub-figure) show differences in reaction times that are much greater than fifty milliseconds – almost 300 milliseconds in the first assessment and approximately 150 milliseconds in the second and third assessments.

Plots of the paired differences in mean thruput (column 2 of Figure 1) show analogous patterns to those of mean reaction times. Specifically, the paired differences in mean thruput during tests of SRT are roughly symmetric about the same number – negative forty – for assessments 1, 2, 3, 4, and 6, and the differences for the fifth assessment are of slightly greater magnitude. Differences in mean thruput in tests of PRT are roughly symmetric about negative ten for all three assessments. Assessments 1 and 3 of CSD show similar distributions of paired differences in mean thruput and assessment 2 shows greater variability in the differences. Finally, the tests of CSL show significant differences in DANA-measured and ANAM-measured thruput that vary in magnitude across the three assessments.

Given the relatively small sample, we formally test for differences between DANA and ANAM measures with the Wilcoxon signed rank test. Table 2 displays the Wilcoxon statistic (W) and p-value for tests of the hypothesis that DANA-measured reaction times are greater than ANAM-measured reaction times by fifty milliseconds in tests of SRT, PRT, and CSD. We did not test this hypothesis for CSL as it was made clear in Figure 1 that the differences for this test are much greater than fifty milliseconds. With the exception of the fifth assessment of SRT, we do not reject the hypothesis of a fifty millisecond difference in mean reaction time.

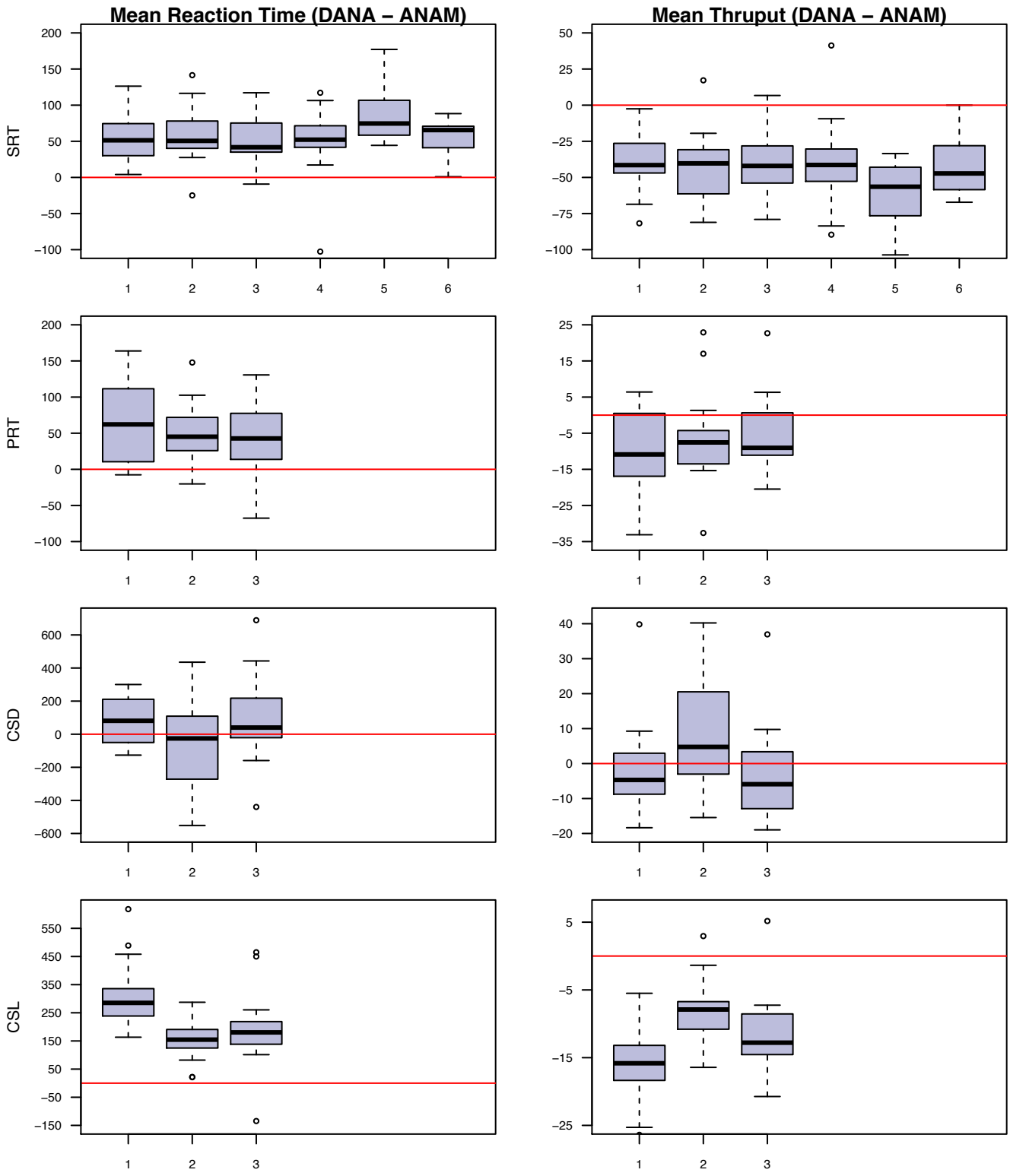


Figure 1: Paired Differences Between DANA and ANAM by Test and Time

Table 2: Wilcoxon Signed Rank Tests for Differences of Fifty Milliseconds in DANA-Measured and ANAM-Measured Reaction Time During Tests of SRT, PRT, and CSD

Test	t	W	**P-Val**
SRT	1	99	0.5798
	2	106	0.3927
	3	72	0.8536
	4	87	0.6441
	5	117	0.0003
	6	75	0.4212
PRT	1	111	0.2837
	2	67	0.6777
	3	53	0.7197
CSD	1	103	0.4683
	2	44	0.1324
	3	64	0.8469

A Supplemental Information

This section provides supplemental information compiled during analysis. Figures 2 and 3 display the distributions of mean reaction time and mean thruput, respectively, by test, time and device. The overall median (ignoring assessment number) for each test, measure and device is shown as a horizontal blue line in each sub-figure. The statistics displayed in these figures along with additional summary statistics are given in Tables 3 and 4. To investigate patterns over time, Figures 4 and 5 display paired differences in mean reaction time and mean thruput, respectively, within device. In these figures, assessments 2, 3, 4, 5, and 6 are compared with the first. Finally, Table 5 displays the Wilcoxon signed rank statistic and p-value for tests of the hypothesis that DANA-measured thruput minus ANAM-measured thruput is equal to μ_0 (given in column 2 of the table) in tests of SRT and PRT. As in the results of tests for differences in reaction time, the tested hypothesis is only rejected in the fifth assessment of SRT.

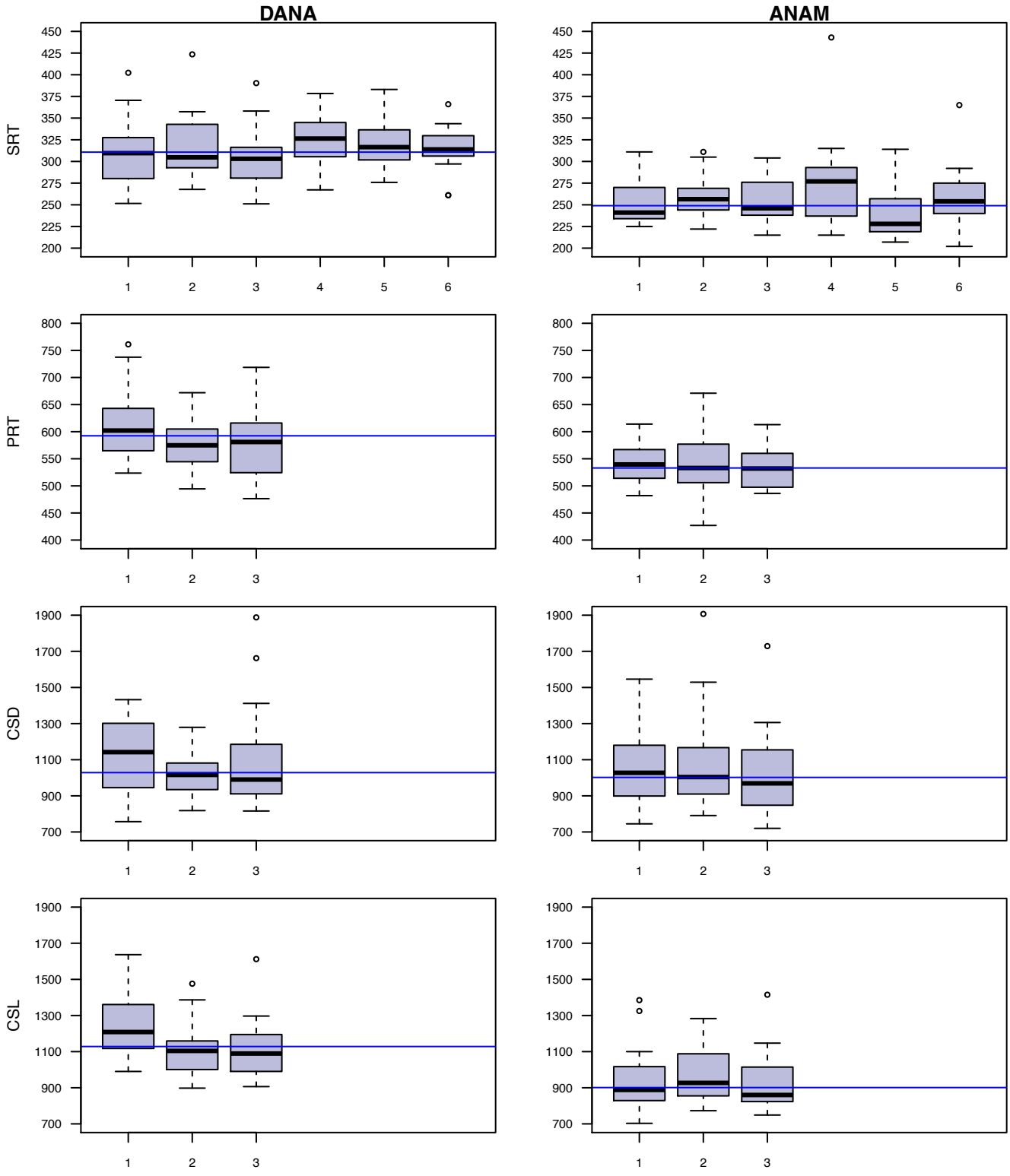


Figure 2: Distribution of Mean Reaction Time by Test, Time, and Device

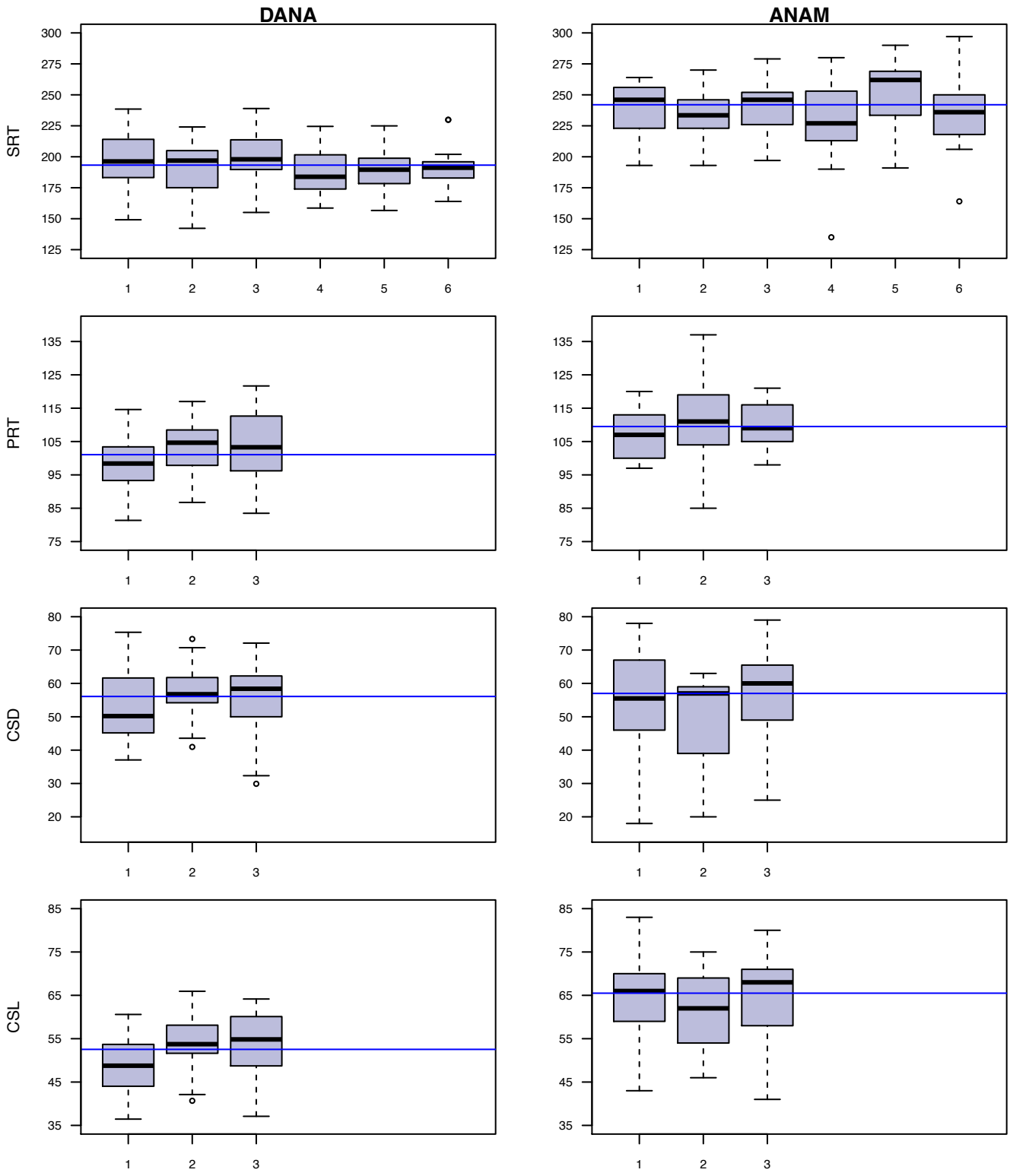


Figure 3: Distribution of Mean Thruput by Test, Time, and Device

Table 3: Summary Statistics for DANA Measures

Measure	Test	Time	n	Min	Q_1	Median	Mean	SD	Q_3	Max
Mean RT	CSD	1	18	757.20	952.00	1142.00	1122.00	202.83	1274.00	1432.00
		2	17	818.30	934.60	1016.00	1021.00	128.79	1082.00	1279.00
		3	15	816.10	911.00	990.20	1113.00	313.96	1185.00	1888.00
	CSL	1	18	990.20	1122.00	1208.00	1252.00	208.81	1360.00	1637.00
		2	17	897.90	1001.00	1104.00	1121.00	166.53	1159.00	1476.00
		3	15	906.40	990.40	1090.00	1121.00	184.84	1195.00	1612.00
	PRT	1	18	523.60	571.50	602.10	617.60	63.72	642.70	761.20
		2	17	494.50	544.60	574.80	577.90	48.47	604.90	671.90
		3	15	476.40	524.40	580.90	574.80	65.68	616.00	718.70
	SRT	1	18	251.60	281.70	309.60	308.20	37.38	325.60	402.30
		2	18	267.80	293.10	304.70	317.20	37.79	341.70	423.50
		3	17	251.10	280.80	303.10	303.20	36.84	316.30	390.40
		4	17	267.20	305.40	326.40	323.90	29.02	344.90	378.30
		5	15	275.80	301.80	316.50	317.90	28.44	336.50	383.00
		6	15	261.00	306.20	313.90	313.60	27.55	329.70	366.00
Mean Thruput	CSD	1	18	37.05	45.29	50.20	52.22	10.39	60.68	75.33
		2	17	40.95	54.21	56.76	57.16	8.67	61.76	73.32
		3	15	29.90	50.00	58.40	54.91	12.28	62.24	72.09
	CSL	1	18	36.45	44.05	48.77	48.61	7.74	53.39	60.59
		2	17	40.68	51.64	53.74	53.76	7.41	58.12	65.94
		3	15	37.10	48.72	54.84	53.84	7.71	60.10	64.16
	PRT	1	18	81.36	93.35	98.40	97.82	8.95	102.80	114.60
		2	17	86.74	97.85	104.60	103.50	7.96	108.50	117.00
		3	15	83.49	96.22	103.30	104.80	11.37	112.60	121.70
	SRT	1	18	149.20	184.30	196.20	197.50	22.63	213.00	238.50
		2	18	142.20	175.60	196.90	191.50	20.71	204.70	224.10
		3	17	155.10	189.70	198.00	200.80	22.98	213.70	239.00
		4	17	158.60	174.00	183.80	187.00	17.65	201.60	224.50
		5	15	156.60	178.40	189.60	190.70	17.66	198.80	224.90
		6	15	164.00	182.80	191.10	193.00	17.74	195.90	229.90

Table 4: Summary Statistics for ANAM Measures

Measure	Test	Time	n	Min	Q_1	Median	Mean	SD	Q_3	Max
Mean RT	CSD	1	18	745.00	909.80	1028.00	1044.00	221.79	1154.00	1546.00
		2	17	791.00	910.00	1004.00	1119.00	304.24	1167.00	1907.00
		3	15	720.00	848.00	969.00	1025.00	265.25	1154.00	1729.00
	CSL	1	18	703.00	834.20	888.00	936.60	181.09	1001.00	1385.00
		2	17	773.00	855.00	927.00	965.90	148.44	1088.00	1283.00
		3	15	749.00	823.50	860.00	931.10	178.00	1014.00	1415.00
	PRT	1	18	482.00	517.50	539.50	545.10	41.79	566.20	614.00
		2	17	427.00	506.00	533.00	536.60	62.34	577.00	671.00
		3	15	486.00	497.50	532.00	532.10	40.04	560.00	613.00
	SRT	1	18	225.00	234.00	241.00	252.90	27.63	267.20	311.00
		2	18	222.00	244.20	256.50	258.40	23.84	268.00	311.00
		3	17	215.00	238.00	246.00	280.80	122.33	276.00	744.00
		4	17	215.00	237.00	277.00	301.00	125.69	293.00	744.00
		5	15	125.00	219.00	228.00	233.60	41.34	257.00	314.00
		6	15	202.00	240.00	254.00	259.20	37.07	275.00	365.00
Mean Thruput	CSD	1	18	18.00	46.50	55.50	54.22	15.90	65.25	78.00
		2	17	20.00	39.00	57.00	49.24	14.16	59.00	63.00
		3	15	25.00	49.00	60.00	57.27	15.73	65.50	79.00
	CSL	1	18	43.00	59.25	66.00	64.56	10.37	69.75	83.00
		2	17	46.00	54.00	62.00	61.71	8.70	69.00	75.00
		3	15	41.00	58.00	68.00	65.13	10.38	71.00	80.00
	PRT	1	18	97.00	101.00	107.00	107.50	7.33	112.80	120.00
		2	17	85.00	104.00	111.00	110.50	12.73	119.00	137.00
		3	15	98.00	105.00	109.00	110.00	7.79	116.00	121.00
	SRT	1	18	193.00	225.20	246.00	237.90	22.89	256.00	264.00
		2	18	193.00	224.00	233.50	234.00	20.59	245.80	270.00
		3	17	197.00	226.00	246.00	240.90	24.23	252.00	279.00
		4	17	135.00	213.00	227.00	227.20	35.77	253.00	280.00
		5	15	191.00	233.50	262.00	251.80	26.65	269.00	290.00
		6	15	164.00	218.00	236.00	235.50	30.05	250.00	297.00

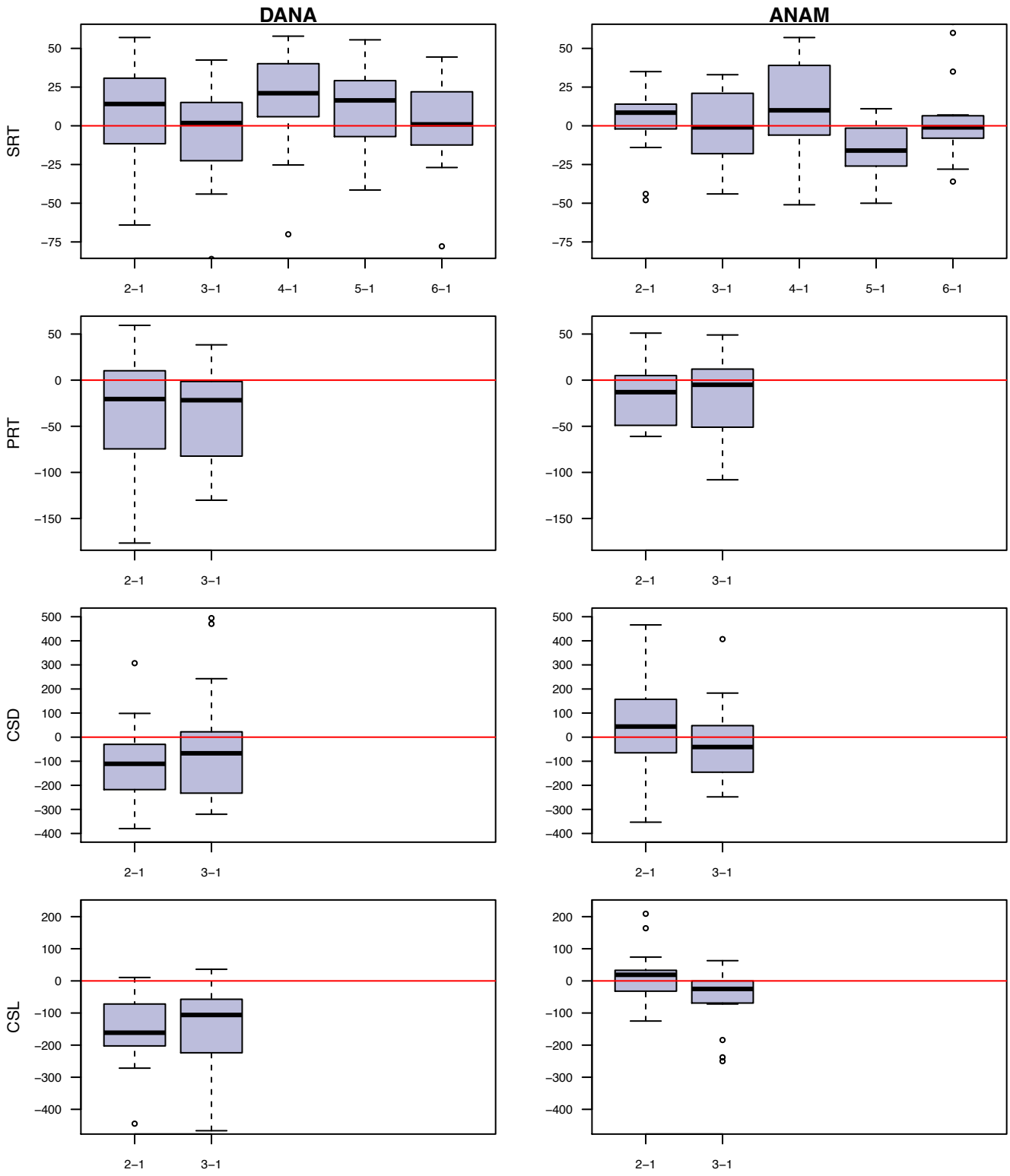


Figure 4: Paired Differences in Mean Reaction Time Within Device

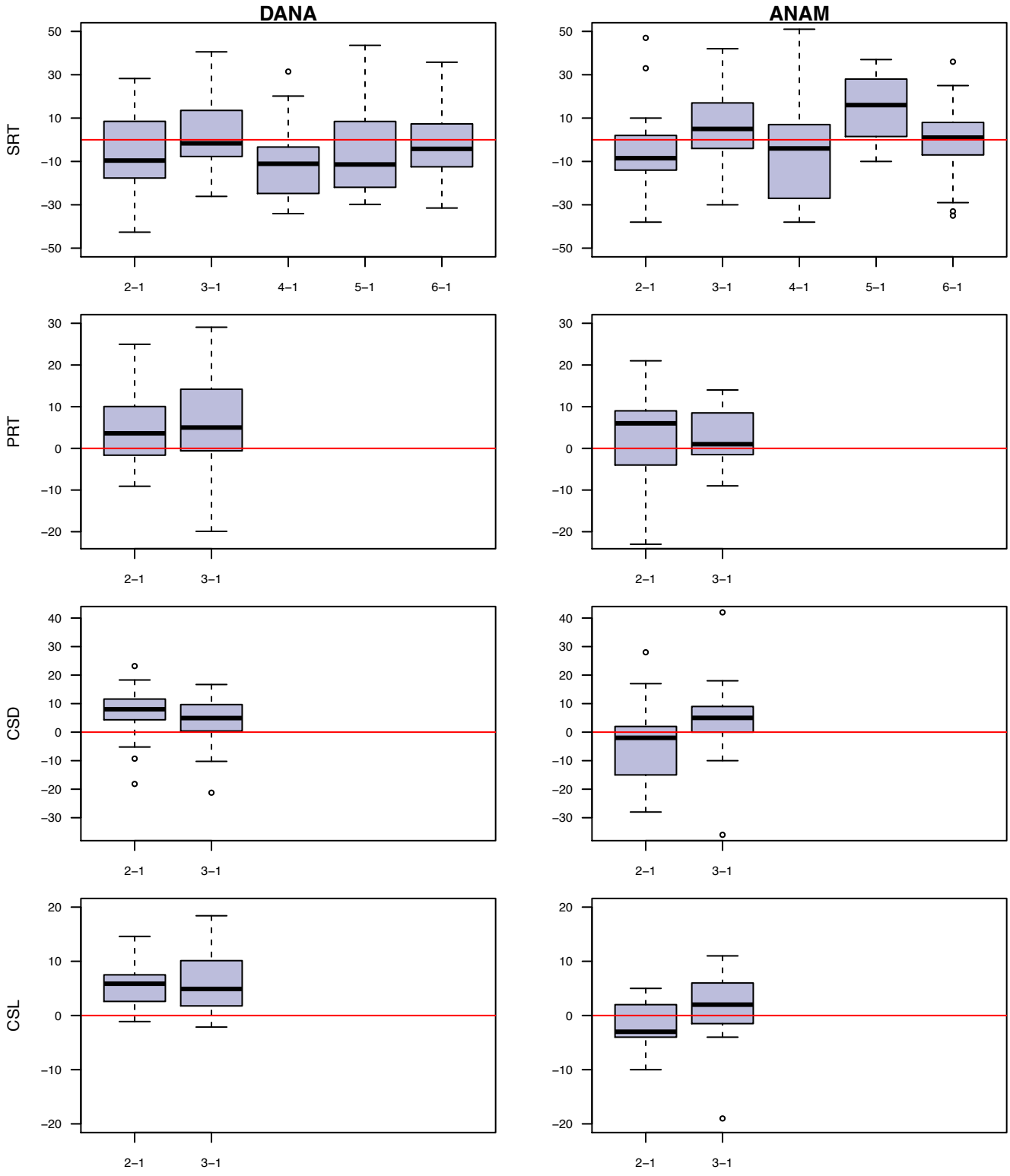


Figure 5: Paired Differences in Mean Thruput Within Device

Table 5: Wilcoxon Signed Rank Tests for Differences Between DANA-measured and ANAM-measured Thruput During tests of SRT and PRT

Test	μ_0	t	W	**P-Val**
SRT	-40	1	84	0.9661
		2	71	0.5509
		3	73	0.8900
		4	68	0.7119
		5	11	0.0034
		6	49	0.5614
PRT	-10	1	93	0.7660
		2	94	0.4307
		3	84	0.1876

Appendix U

MEMORANDUM

To: Cori Lathan
From: Helaine Resnick
Re: Altitude Data
Date July 7, 2013
Cc: Lawrence Wolpert

This memo summarizes findings from analysis of the DANA "altitude data." This set of analyses addressed a number of questions pertaining to an experiment in which DANA was used at different altitudes to assess various features of cognitive function. A number of questions related to specific variables that were collected in this experiment are listed below in **bold**, and the responses to each are provided immediately below the question. Some questions are supported by supplemental graphics that illustrate the summary of findings. A number of the questions are inter-related.

There was interest in understanding whether using mean values yielded significantly different results from use of median values. This interest was based in concerns about the appearance of occasional outlying values and the potential impact that outliers may have on results. Thus, in many analyses, we present results using both mean and median SRT values. In general, the conclusions that are drawn are similar, although it is clear that outliers do influence the distributional properties of the data.

The data set that was used in these analyses contained some missing data. In some cases, individual subjects did not have SRT data at each altitude; in other cases, participants did not have repeat administrations of SRT. Because part of these analyses involved calculation of new variables based on data in the spreadsheets that were provided, there are some instances where missing data resulted in individual participants being dropped from some of the analyses. These missing observations do not materially impact the overall findings that are presented below.

1. **Does DANA SRT detect cognitive deficit measured by SRT as altitude increases?**
   Yes. Anthrotronix already had reason to believe that DANA SRT provides useful information on cognitive changes with varying altitude. Our analyses support this conclusion.

   The chart below shows box and whisker plots for the variable "MeanCorrRT" across altitudes. These show quartiles, minima and maxima. Keep in mind that the number of subjects contributing data is quite small at the end of the protocol relative to the beginning, and that the overall sample is relatively modest in size. The left panel shows means for the first SRT administration (outliers are apparent), and the right panel shows means for the second administration. We see two trends: First, SRT becomes significantly less favorable on the first day at 17,000 feet (ALT1), and it tends to go back toward baseline levels by day 16 at high altitude. The second finding is that the second administration of the SRT protocol (ADMIN2)

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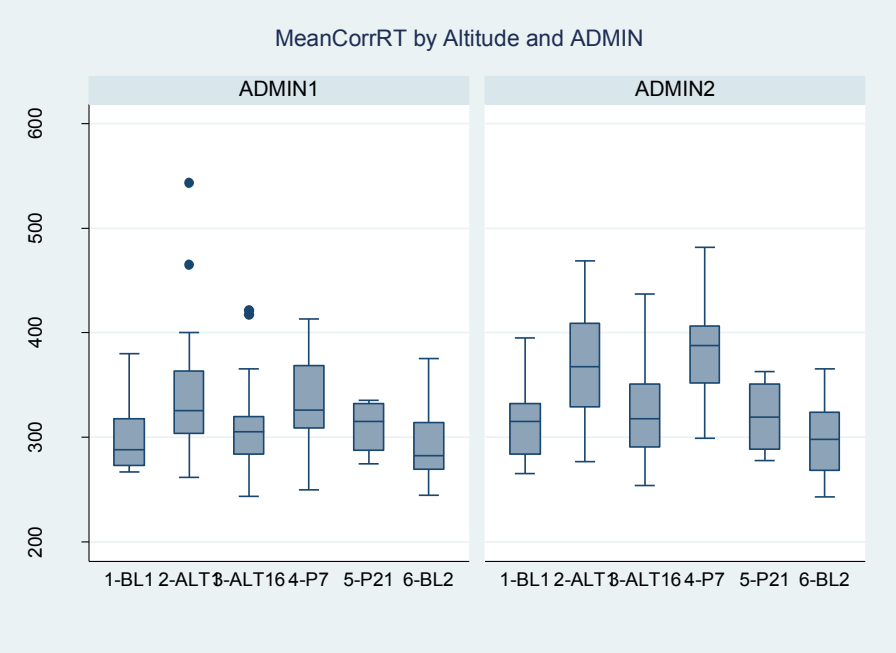
tends to have less favorable values at each altitude relative to the first administration (ADMIN1). This finding is explored further below.



The chart below shows a corresponding set of analyses using median SRT, rather than mean SRT. A similar pattern is observed for median values, both with regard to worsening performance at ALT1, improvement at ALT16, and in terms of less favorable performance on the second administration of the SRT protocol at all altitudes.

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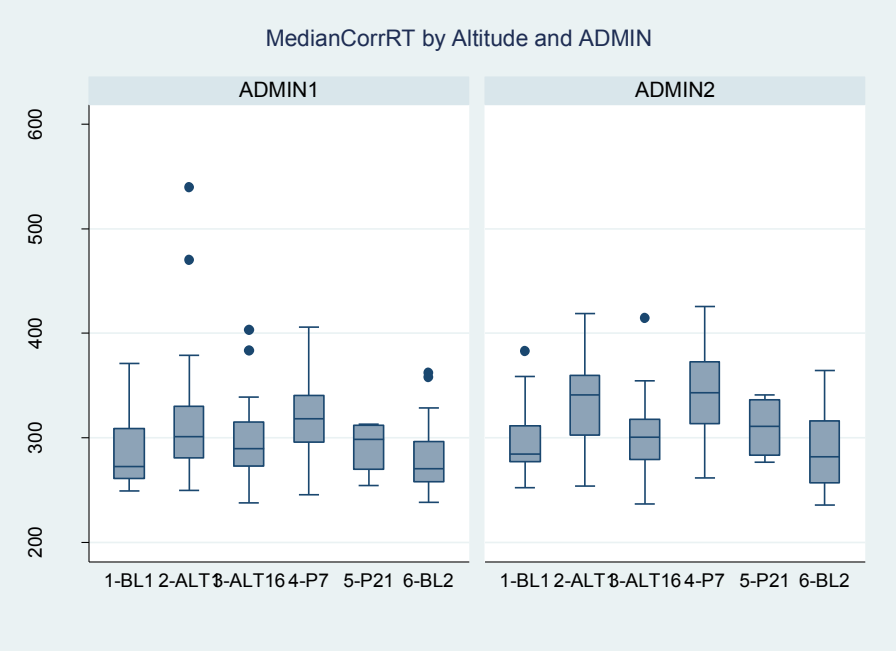

There was a related question regarding “retention of acclimation.” That is, do participants retain cognitive function after having come down to sea level and then going back up again. These questions can be explored to some degree with data that were collected at P7 and P21, the time points with relatively few observations. Nonetheless, inspection of the box plots above indicates that among participants for whom data were available, performance at P7 was actually less favorable than ALT1 and certainly less favorable than BL1. Once again, ADMIN2 results appear slightly less favorable than ADMIN1 results at P7.

2. **Does a second administration (trial) of the DANA SRT protocol provide additional useful information on cognitive function beyond the first measure, and if so, how does this additional information "behave" at sea level (BL1), at the first day at high altitude, and at the 16th day at high altitude (acclimation)? Are the differences uniform across the points on the protocol timeline?**

The second SRT administration provides useful information. The box plots suggest that the overall distribution of SRT data is less favorable during the second administration. However, it is instructive to look at the data on an individual basis to determine if this pattern is consistent. We can do this by creating two new variables “ADMIN2-ADMIN1” for both means and medians. If this difference is generally greater than zero overall and for each individual, we may conclude that the second administration yields consistently less favorable results than the first. The chart below shows the overall distribution of the two difference variables (means and medians) at each altitude. It is evident that the overall value exceeds zero for both the means and medians, with some variability due to small sample size and outliers. The impact of the outliers (shown as dots) can be seen for the difference variables in much the same way as they could for the earlier

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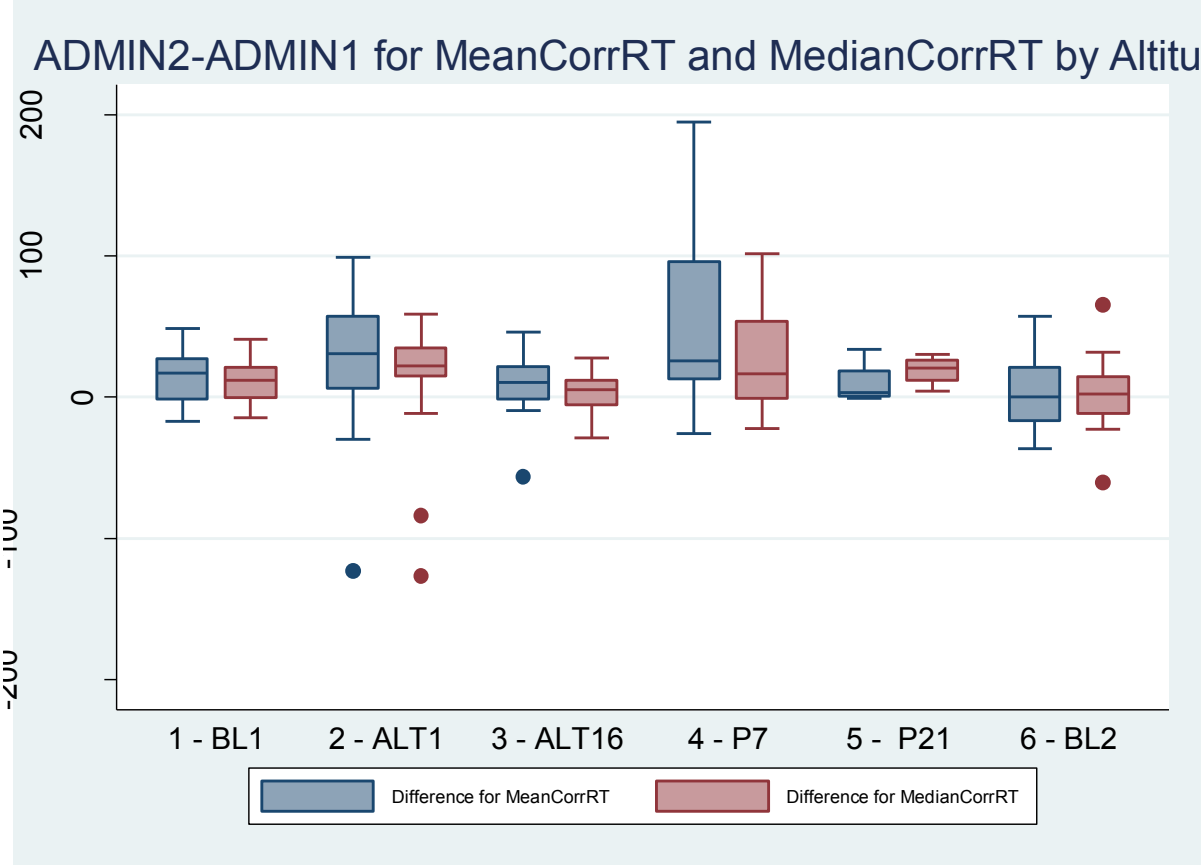
analyses. Once again, it is important to note that there is less data available after ALT16, so those results should be interpreted with particular caution. Nonetheless, P7 and P21 difference variables are both above zero.



Another way to look at the data is to examine differences on the individual level at each altitude. In many cases this is not practical (or advised) because such anecdotal findings are often misleading and rarely robust. In this case, we have a relatively small sample size as well as missing data at various points in the protocol. This makes it easy to show individual level data on a single chart with the understanding that we are not engaged in inferential statistics, but rather, we are looking to get a deeper understanding of how various measures behave under different experimental circumstances.

The charts below show these individual-level ADMIN2-ADMIN1 difference data for both means and medians. The first two charts look at these differences by putting BL1 and ALT1 next to one another on the same graph. For participant number 16 for example, the mean difference in SRT at baseline was 16 ms, but at ALT1 it was 57 ms. In most, but not all participants, mean

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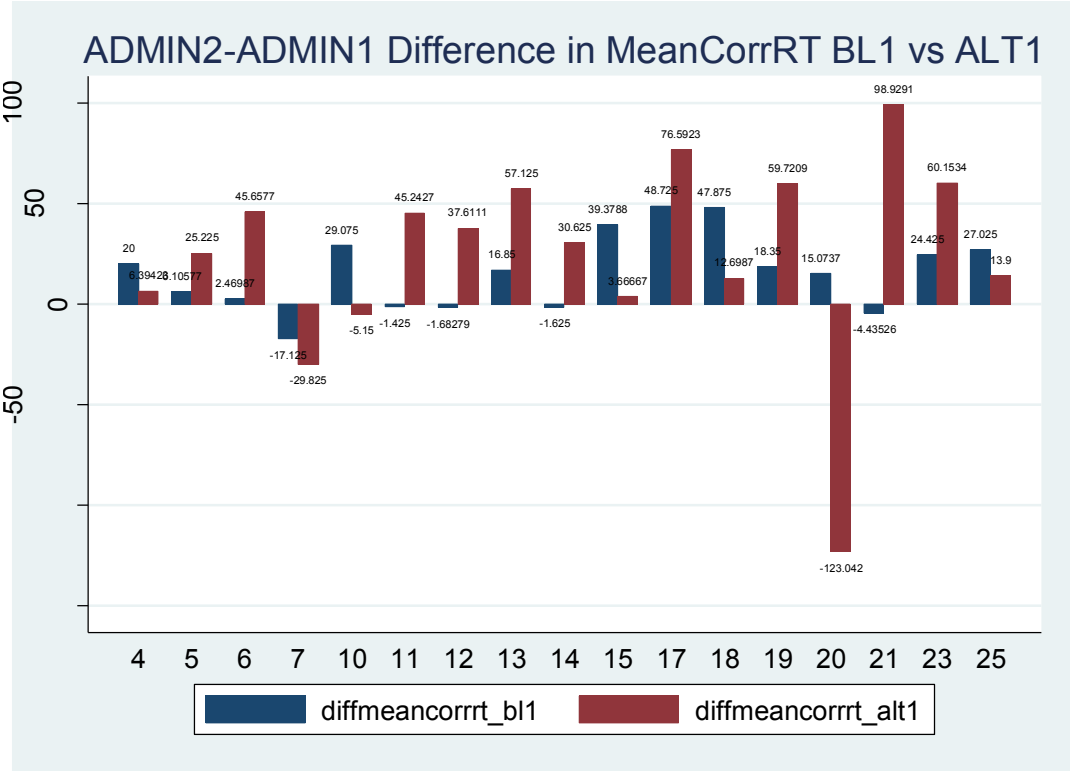
differences at both BL1 and ALT1 were greater than zero, suggesting poorer performance on the second administration. Further, in many, but not all cases, the differences at ALT1 were greater than they were for BL1, suggesting *exacerbation of differences* under the experimental stress of altitude. Analysis of median values showed the same general findings. The impact of the outliers is very apparent in graphs of individual-level data. In fact, we believe that these are the participants that Anthrotronix personnel indicated would not be included in routine data analyses because of their suspect measures.



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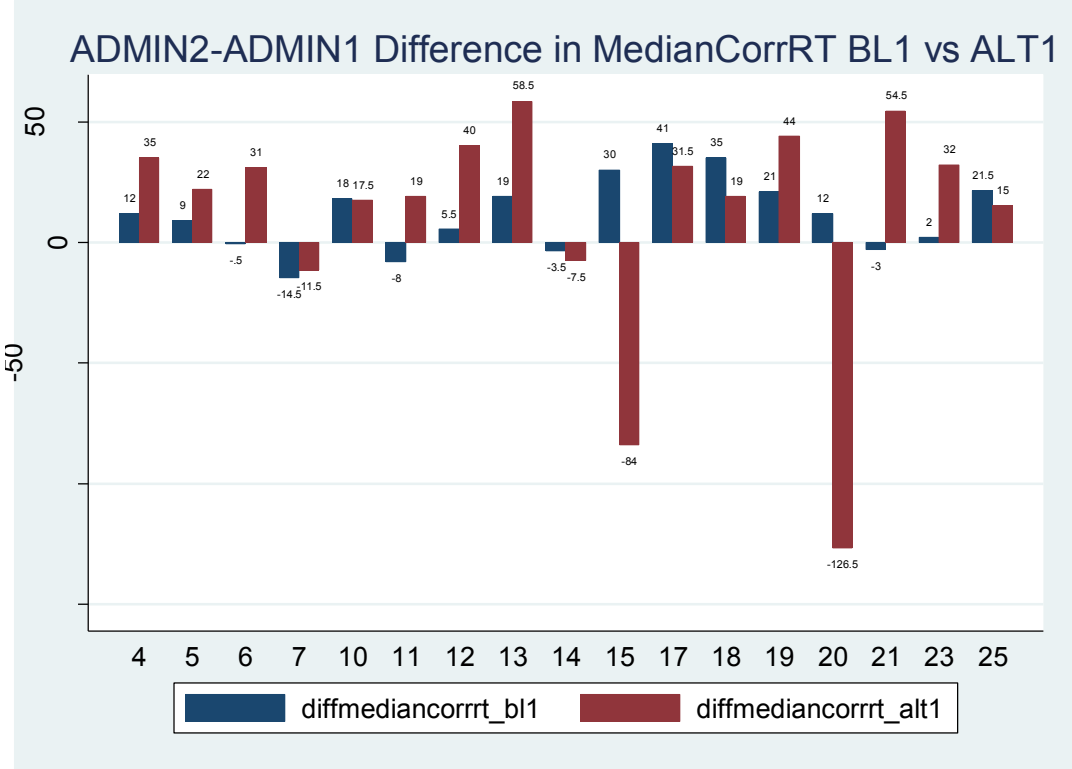

The next two plots show individual-level mean and median differences in SRT (ADMIN2-ADMIN1), but place findings for ALT1 next to ALT16 to illustrate how these variables behave in relation to the issue of acclimation at high altitude. We see the same pattern indicating that differences are generally greater than zero for most participants, suggesting poorer performance on the second SRT administration. But when we look at ALT1 and ALT16, we see that for differences in both means and medians, most people perform much worse at ALT1 than at ALT16, as we would expect.

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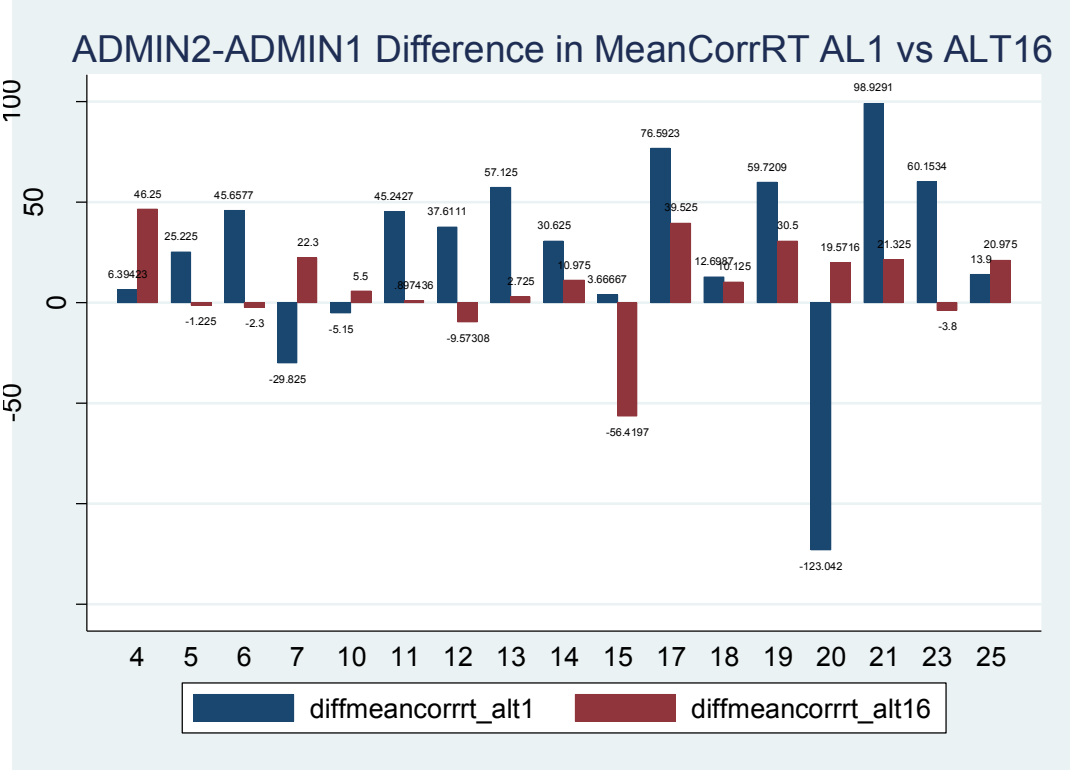

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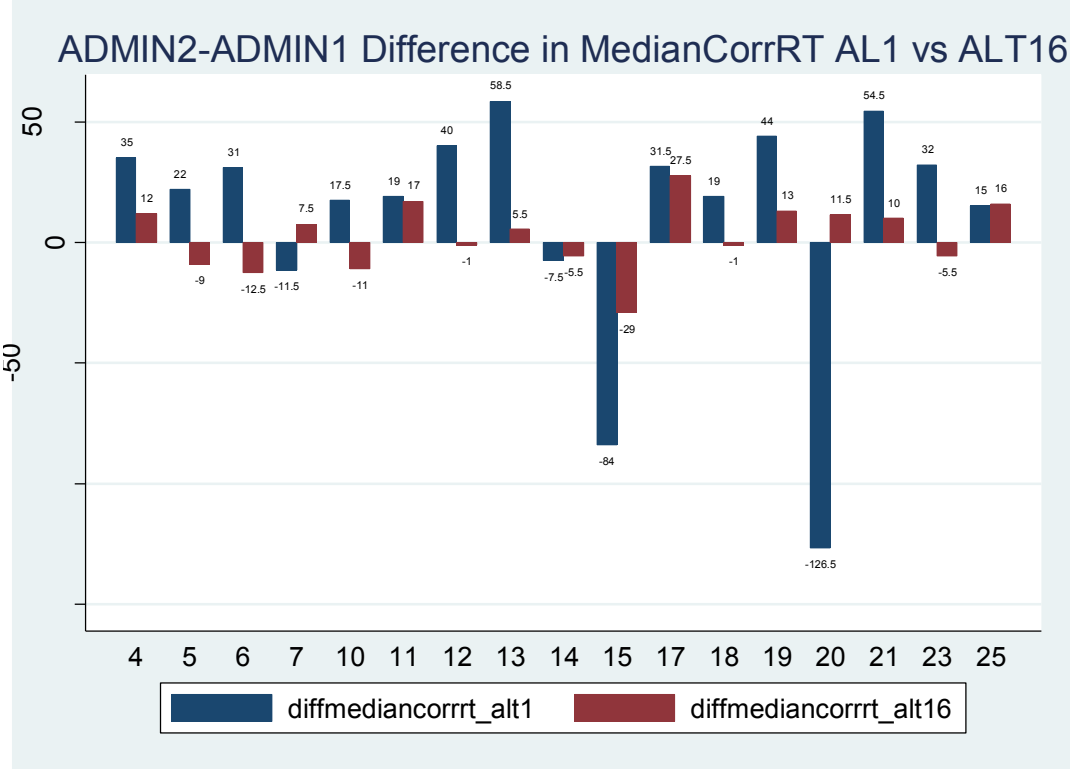

Overall, the results of ADMIN2 are sufficiently different from ADMIN1, both in distribution of the data and in systematically higher response times at all altitudes to suggest that ADMIN2 provides addition information beyond that which is offered by ADMIN1. ADMIN2 also had a wider range of Q1/Q3 (25th and 75th percentiles) and minimums and maximums at each altitude compared to ADMIN1, indicating greater spread.

3. **Which measure of reaction time is the most sensitive in picking up declining cognitive function as altitude increases? Is it ADMIN1, ADMIN2 or ADMIN2-ADMIN1?**

We can probably conclude that ADMIN1 is not the best way to assess reaction time because we know that ADMIN2 is generally worse. As a result, the difference between ADMIN2 and ADMIN1 is going to be greater than zero in most cases. Thus, we are left with the question of whether to use ADMIN2 or ADMIN2-ADMIN1 to assess cognitive decline. For the sake of simplicity, in a research setting in which outliers are removed from the data set with certainty, ADMIN2 is likely to provide a good assessment of cognitive decline across changing altitude. Further, analysis of the difference between the two administrations can be viewed as a tool that helped provide a rationale for using the second administration, but *using the difference itself is not informative for understanding cognitive function*-we need to use a variable that uses the full range of SRT values, not just a plausible range of differences. One way to think about this problem is to compare it to office-based blood pressure measurements. In many cases, patients are anxious

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on their first measure, making it artificially elevated. As a result, a second measure is taken and that measure if often used. In some cases, the average of the two measures is preferred. In no cases is there a clinical application for the difference in two blood pressure measures. The same principle holds true for the second SRT administration. If use of both ADMIN1 and ADMIN2 is desired, then exploration of the question of averaging the two measures is more useful than using the difference between the two.

4. **Are the ADMIN1 and ADMIN2 tests similar, or does ADMIN2 show fatigability (not able to sustain the response)? If non-zero difference are observed, is this fatigue or indifference to performing the test a second time?**

   As noted above, ADMIN2 shows more dispersion and higher response times on the various charts and box plots for both means and medians compared to ADMIN1. The higher response times could indicate participant fatigue/difficulty in sustaining high performance, or indifference toward the second administration. It is not possible to absolutely distinguish a participant who is "annoyed" with having to do the protocol twice from one who is truly fatigued. However, the consistency of the patterns with regard to ADMIN2 vs ADMIN1 suggest that participants may indeed be unable to sustain their SRT performance levels over repeated administrations of the testing. Removal of outliers from the data set would likely make these patterns even more homogenous, thereby supporting the idea that the data reflect true fatigue.

5. **When going from BL1 at sea level to ALT1 followed by ALT16 after a period of stabilization, how much acclamation did participants retain at ALT16? Is there an impact on reaction time by the end of the experiment?**

   ALT16 results consistently resembled those at BL1, suggesting that participants acclimated to altitude by day 16. The difference in MeanCorrRT box plot medians for response times show that they decreased (improved) after a period of adjustment at that altitude. Response times were clearly worse on the first day at 17,000 ft compared to BL1. However, by ALT16, response times had regressed toward BL1 values. Along the same lines, P7 had a higher median response time than P21 compared to baseline. However, this is based on a very small number of observations and should be interpreted with extreme caution.

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MEMORANDUM

To: Cori Lathan
From: Helaine Resnick
Re: Altitude Data
Date July 18, 2013
Cc: Lawrence Wolpert

This memo provides additional thoughts on several questions that were posed in response to our memo dated July 7, 2013. Those questions are in bold, followed by non-bolded responses.

Page 1: Looking at the data - medians properly classified the subjects with the "bad" data better than the mean data but frankly those subject admins would never stay in any analysis since they had so few trials. If they can't do the test, they are either malingering or sick and it is pretty easy to distinguish!

Agreed, the median did a better job of identifying outliers. Since this was a qualitative and not a statistical analysis, the outliers were retained for the box plots and other results. Regardless, the outliers do not participate in the calculation of the percentiles including the actual median values. Note that all of the outliers were due to ID 15 and ID 20.

Page 3: Are you saying P7 is actually WORSE than ALT1?
A key question is - is there any retention of acclimations from ALT16 to P7. You are saying no.

ALT1 had a lower median response time compared to P7 as highlighted below. The same can be seen for ALT16-those values are lower than P7. However, P7 is based on few observations.

Comparison of ALT1 to P7 - ALT1 has a lower response time for ADMIN1 & ADMIN2

ADMIN	Altitude	Box Plot Medians - excludes outliers from the calculation of the percentiles
ADMIN1	ALT1	301.0
ADMIN1	P7	318.5
ADMIN2	ALT1	341.0
ADMIN2	P7	343.0

Comparison of ALT16 to P7 - ALT16 has a lower response time for ADMIN1 & ADMIN2

ADMIN	Altitude	Box Plot Medians - excludes outliers from the calculation of the percentiles

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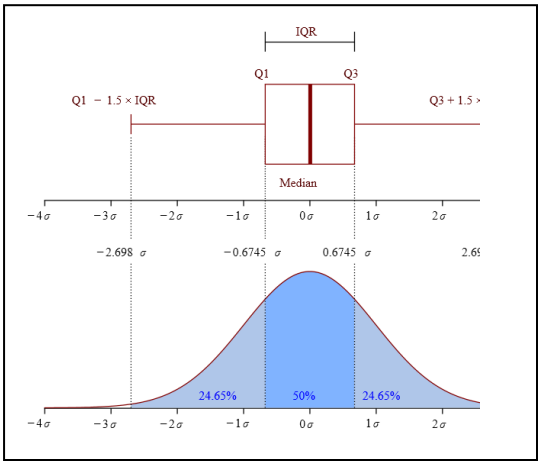
ADMIN1	ALT16	290.0
ADMIN1	P7	318.5
ADMIN2	ALT16	300.5
ADMIN2	P7	343.0

Page 4: Looking at individuals and "classifying" them is exactly what you do with hypoxic subjects from a behavioral perspective. Not sick, sick, very sick. If we could predict from this data which ones fell in to which category, that would be cool!

Below are some thoughts about classifying the individuals into categories for hypoxia. These ideas may or may not be the most appropriate approaches to address the question. Further evaluation can be done to identify the best statistical method(s) to meet your objective if you wish to pursue this idea with the data that are available.



One approach would be to use percentiles to classify the groups by using a combination of percentiles and the interquartile range (IQR). A diagram of the box plot with the corresponding information for the distribution of data is provided for reference. The IQR corresponds to a little less than +/- one standard deviation. Anything above Q3 would be considered either sick or very sick. Two standard deviations could be used as the threshold for very sick.

Another approach is to perform regression analysis. However, the low sample size may be a problem. Since regression analysis is really modeling the data collected, a predictive model would require a second dataset to confirm the model or the data would have to be split into two datasets to develop and validate the model.

A third possibility would be to use nonparametric analysis to determine the category of not sick, sick or very sick. This might be a better approach due to the small sample size.

Page 8: I don't know why you would say this - the difference may be much more reflective of cognitive function than the actual value. The actual value doesn't tell you anything without a comparison either (eg. the difference from baseline).

We were not referring to differences from baseline, but differences at a single point in time between two separate administrations. The statement on page 8 was based on comparing the information on MeanCorrRT for ADMIN1 and ADMIN2 separately versus looking at the difference between ADMIN2-ADMIN1. While both methods use the same data, the first method allows the individual reviewing the results to visually compare ADMIN1 versus ADMIN2 and determine if the results are similar or different for the response time and the distribution of response times for each

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ADMIN. ADMIN2-ADMIN gives a direct measure of the difference in response time but may be more difficult to look at differences in patterns between ADMIN1 and ADMIN2 response times. Essentially, it may be more of a preference in how one thinks about data and what is needed to address the question of cognitive function.

Page 8: Totally not valid analogy! A much better one, although not perfect is a thermometer. You never take it a 2nd time. The measurement is expected to be valid on first try unless some strange circumstance. SRT is much more like that - a reflex - either you are malingering or sick! There is no/little learning or relaxing. In fact, a little stress/adrenaline would be more likely to make the reaction time faster, not slower, thereby decreasing the diff b/n srt1 and srt2.

Agreed that your analogy is better-we will stick to statistics!

Page 9: This is true ONLY for baseline. Actually what is recommended for neurocog baseline is take it 3 times and take BEST score

Ok.

Page 9: Outliers - are you referring to the 3 ALT1 admins that should be deleted?

The calculation of the box plot percentiles, including the median, do not include the outliers. The three "outliers" you mention are the green lined data in the SRT spreadsheet provided for analysis? If so, the "outlier" for MeanCorrRT=480 for ALT1, ADMIN2, ID 12 is not an outlier on any of the box plots presented on pages 2-4.

Page 9: The "retention" question is for P7 and P21. After 16 days of acclimation, they go back down to about 5,000 for 7 or 21 days. P7 is back at altitude after 7 days and the question is are they more like ALT1 or ALT16. I think they are more like ALT16 - is that true?

For both ADMIN1 and ADMIN2, the MedianCorrRT box plot median for P7 is more similar to ALT1 than ALT16.
For both ADMIN1 and ADMIN2, the MedianCorrRT box plot median for P21 is more similar to ALT16 than ALT1.

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Appendix V: Power Analysis Calculations for Normative Data

SUMMARY

Collection of data from 50 normal participants (no head injury, currently healthy, non-deployed) in each of several age categories will provide sufficient information to define thresholds of normal values for DANA subscales. Our pilot data not only suggest that 50 participants is a conservative number, but they also indicate that this number is sufficient to provide a favorable trade-off among considerations as diverse as project operation costs, clinical sensitivity and potential future applications of DANA as a screening and triage instrument.

BACKGROUND AND STATEMENT OF FACT

We were asked to respond to concerns regarding the absence of a "power analysis" underpinning our recommendation to enroll 50 individuals per age group as part of a larger effort to establish a normative database of DANA values. Two points should be recognized:

1. A power analysis is one of a number of standard practices that are used to design clinical studies where *the goal is to engage in hypothesis testing*. In many cases, such a hypothesis aims to determine if two groups are statistically distinct from one another (e.g. a randomized clinical trial to test the effectiveness of a new therapy relative to standard of care). Normative databases are not used to compare groups in this way. As a result, classic power analyses do not apply in this setting.

2. There is no "standard number" of individuals that is universally required, recommended or recognized for establishment of a normative database. Nonetheless, it is recognized that "more information is better" until the point of diminishing returns is reached with regard to precision. Identifying the point at which this condition is met is a subjective process involving assessment of all available evidence combined with clinical judgment.

RATIONALE FOR RECOMMENDATION OF 50 INDIVIDUALS PER AGE GROUP

The attached spreadsheet, which is based on actual DANA reaction time data, illustrates how we arrived at a recommendation of 50 people per group. The spreadsheet is divided into five age groups in a manner that reflects how we anticipate enrolling participants into the normative database study. The reaction time data (mean=306.75 [column A], s.d.=46.56 [column B]) for the youngest age group (age <30) is based on pilot data collected at LeJeune and 29 Palms. Column C of the spreadsheet examines scenarios in which the enrollment for a hypothetical normative database varies from a minimum size of 10 individuals to a maximum of 100 individuals in each age group. Using the standard deviation and varying sample sizes, we calculate the standard error for each scenario, a value that appears in column D. It is evident that the standard errors of these normative database scenarios decrease in an expected pattern as sample size increases.

The goal of a normative database is to identify threshold values at which individuals are no longer considered to be within a normal, or expected range of values. By design, the pilot data on which our sample size estimates are based consist entirely of young, normal individuals, and are therefore tightly distributed. Against the backdrop of these highly informative pilot data, we must determine at what threshold we wish to define an individual as being outside the normal range in the future. Because all DANA measures are unidirectional with respect to performance (e.g. "higher is better" or "lower is better"), we are only concerned with upper or lower thresholds of normal, but not both. In the reaction time example, we are concerned with identifying an upper threshold of normal because shorter reaction times indicate better performance. Although the converse is true for other DANA measures, the following approach applies equally to both measurement settings.

A rigorous strategy to identify and evaluate upper thresholds of normal is to calculate the value of reaction times or other DANA parameters that correspond to critical locations on the upper end (right hand side) of the reaction time distribution. These locations correspond to critical values of the *t* distribution and are shown in Columns E through H of the spreadsheet. For example, 10% of data on the *t* distribution fall beyond (to the right of) 1.372 and 0.5% of the data fall beyond 3.169. We can use these critical *t* values to calculate actual DANA values such that we can identify thresholds beyond which 10%, 5%, 1% or only 0.5% of the data are likely to fall. We can then label individuals who fall in these parts of the curve "abnormal" depending on how conservative we wish to be with this definition. Because these threshold calculations involve the standard error (which is based on sample size), they will change in response to changing sample sizes. Thresholds of interest are shown in columns J through M of the spreadsheet, and are the basis of our recommendation to enroll 50 individuals per age group.

It is evident that in scenarios using smaller sample sizes, the likelihood of a false negative result increases. For example, if only 10 people in the <30 age group were enrolled in the normative database study, 99.5% of the data in this group would be expected to fall below a threshold of 353 ms, and these individuals would be considered normal. In contrast, a normative database that includes 50 individuals would place that same threshold at 324 ms, a level that will result in a larger number of individuals falling beyond the normal threshold value. This will reduce the frequency with which the normative database will result in false negatives. Another way to express this concept is to say that the database's sensitivity will increase. Clinically, increasing sample size for a normative database will result in DANA being able to distinguish between normal and abnormal individuals with greater precision. The advantages of such a result are obvious.

Examination of threshold values across sample size scenarios indicates that regardless of what threshold of normal (e.g. >90% or >99.5%) is of interest, enrollment of additional subjects yields diminishing returns on precision after approximately 50 individuals. That is, the relative contribution of participants to the precision of the database is most evident at sample sizes up to 50, at which point the calculated thresholds change very

little. As emphasized above, however, sample sizes smaller than 50 will result in a potentially unacceptable number of false negatives and low sensitivity, a property of the database that will have obvious clinical and tactical implications.

DANA pilot data did not include sufficient numbers of older service members to yield usable information for calculations similar to those in the <30 age group. As a result, threshold values for the older groups were projected based on application of two assumptions to the data for the <30 age group. Using reaction time as an example, we assumed that the mean value would increase (i.e. performance would become less favorable) by 10% with each increasing age group. We also assumed that the standard deviation would increase (i.e. the distribution would become more spread out) by 10% with each increasing age group. Using these assumptions, which we believe are extremely conservative, we nonetheless see that enrollment of 50 individuals in the older age groups results in appropriate levels of precision with respect to estimated threshold values and that enrollment of additional individuals exceeds the point of diminishing returns.

CONCLUSION

DANA pilot data suggest that enrollment of 50 normal (no head injury, currently healthy, non-deployed) individuals per age group into the normative database study will yield sufficient data to calculate age-specific thresholds for DANA values that can be used to distinguish normal from abnormal individuals. Based on the data that are currently available to us, we believe that enrollment of fewer than 50 individuals will result in unacceptably high numbers of false negatives and low sensitivity, and enrollment of more than 50 people will not add appreciably to the precision of the database with regard to its utility as a screening and triage instrument.

Means and standard deviations are based on 10% inflation from the <30 age group. Any numbers can be inserted for thc

				Critcal Values of t			
Mean	s.d	Samp Sz	SE	alpha=.10	alpha=.05	alpha=.025	alpha=.005
						Age <30	
306.75	46.56	10	14.724	1.372	1.812	2.228	3.169
306.75	46.56	20	10.411	1.325	1.725	2.086	2.845
306.75	46.56	30	8.501	1.310	1.697	2.042	2.750
306.75	46.56	40	7.362	1.303	1.684	2.021	2.704
306.75	46.56	50	6.585	1.299	1.676	2.009	2.678
306.75	46.56	60	6.011	1.296	1.671	2.000	2.660
306.75	46.56	70	5.565	1.294	1.667	1.994	2.648
306.75	46.56	80	5.206	1.292	1.664	1.990	2.639
306.75	46.56	90	4.908	1.292	1.670	1.990	2.639
306.75	46.56	100	4.656	1.290	1.660	1.984	2.626
						Age 30-34	
337.4	51.2	10	16.191	1.372	1.812	2.228	3.169
337.4	51.2	20	11.449	1.325	1.725	2.086	2.845
337.4	51.2	30	9.348	1.310	1.697	2.042	2.750
337.4	51.2	40	8.095	1.303	1.684	2.021	2.704
337.4	51.2	50	7.241	1.299	1.676	2.009	2.678
337.4	51.2	60	6.610	1.296	1.671	2.000	2.660
337.4	51.2	70	6.120	1.294	1.667	1.994	2.648
337.4	51.2	80	5.724	1.292	1.664	1.990	2.639
337.4	51.2	90	5.397	1.292	1.670	1.990	2.639
337.4	51.2	100	5.120	1.290	1.660	1.984	2.626
						Age 35-44	
371.1	56.3	10	17.804	1.372	1.812	2.228	3.169
371.1	56.3	20	12.589	1.325	1.725	2.086	2.845
371.1	56.3	30	10.279	1.310	1.697	2.042	2.750
371.1	56.3	40	8.902	1.303	1.684	2.021	2.704
371.1	56.3	50	7.962	1.299	1.676	2.009	2.678
371.1	56.3	60	7.268	1.296	1.671	2.000	2.660
371.1	56.3	70	6.729	1.294	1.667	1.994	2.648
371.1	56.3	80	6.295	1.292	1.664	1.990	2.639
371.1	56.3	90	5.935	1.292	1.670	1.990	2.639
371.1	56.3	100	5.630	1.290	1.660	1.984	2.626
						Age 45-54	
408.2	61.9	10	19.574	1.372	1.812	2.228	3.169
408.2	61.9	20	13.841	1.325	1.725	2.086	2.845
408.2	61.9	30	11.301	1.310	1.697	2.042	2.750

408.2	61.9	40	9.787	1.303	1.684	2.021	2.704
408.2	61.9	50	8.754	1.299	1.676	2.009	2.678
408.2	61.9	60	7.991	1.296	1.671	2.000	2.660
408.2	61.9	70	7.398	1.294	1.667	1.994	2.648
408.2	61.9	80	6.921	1.292	1.664	1.990	2.639
408.2	61.9	90	6.525	1.292	1.670	1.990	2.639
408.2	61.9	100	6.190	1.290	1.660	1.984	2.626

Age 55-64

449	68.1	10	21.535	1.372	1.812	2.228	3.169
449	68.1	20	15.228	1.325	1.725	2.086	2.845
449	68.1	30	12.433	1.310	1.697	2.042	2.750
449	68.1	40	10.768	1.303	1.684	2.021	2.704
449	68.1	50	9.631	1.299	1.676	2.009	2.678
449	68.1	60	8.792	1.296	1.671	2.000	2.660
449	68.1	70	8.140	1.294	1.667	1.994	2.648
449	68.1	80	7.614	1.292	1.664	1.990	2.639
449	68.1	90	7.178	1.292	1.670	1.990	2.639
449	68.1	100	6.810	1.290	1.660	1.984	2.626

ɔse values.

	Threshold for "normal"			
	90% of data	95% of data	97.5% of data	99.5% of data
	326.951	333.429	339.554	353.409
	320.545	324.709	328.468	336.370
	317.886	321.176	324.108	330.127
	316.342	319.147	321.628	326.656
	315.303	317.786	319.978	324.384
	314.540	316.794	318.772	322.739
	313.951	316.027	317.847	321.486
	313.476	315.412	317.109	320.487
	313.091	314.946	316.517	319.702
	312.756	314.479	315.988	318.977
	359.614	366.738	373.473	388.709
	352.569	357.149	361.282	369.971
	349.646	353.263	356.488	363.106
	347.948	351.033	353.761	359.290
	346.806	349.536	351.947	356.791
	345.966	348.445	350.620	354.982
	345.319	347.601	349.602	353.605
	344.796	346.925	348.791	352.507
	344.373	346.413	348.140	351.643
	344.005	345.899	347.558	350.845
	395.527	403.360	410.766	427.520
	387.781	392.816	397.361	406.916
	384.565	388.543	392.090	399.367
	382.699	386.091	389.091	395.170
	381.443	384.444	387.096	392.422
	380.520	383.245	385.637	390.434
	379.808	382.317	384.518	388.919
	379.233	381.574	383.626	387.711
	378.767	381.011	382.910	386.761
	378.363	380.446	382.270	385.884
	435.056	443.669	451.812	470.232
	426.540	432.076	437.073	447.578
	423.005	427.378	431.277	439.279

420.953	424.682	427.980	434.665
419.571	422.872	425.787	431.643
418.557	421.553	424.183	429.457
417.774	420.533	422.953	427.791
417.141	419.716	421.972	426.464
416.630	419.096	421.184	425.419
416.185	418.475	420.481	424.455

478.546	488.022	496.980	517.245
469.177	475.268	480.765	492.323
465.288	470.099	474.389	483.192
463.030	467.133	470.761	478.115
461.510	465.141	468.348	474.791
460.394	463.691	466.583	472.386
459.533	462.569	465.230	470.553
458.837	461.669	464.151	469.093
458.274	460.988	463.285	467.944
457.785	460.305	462.511	466.883

Transitioning the Defense Automated Neurobehavioral Assessment (DANA) Tool to Operational Use (DANA-RIF) Appendix W

Award Number W81XWH-12-C-0204

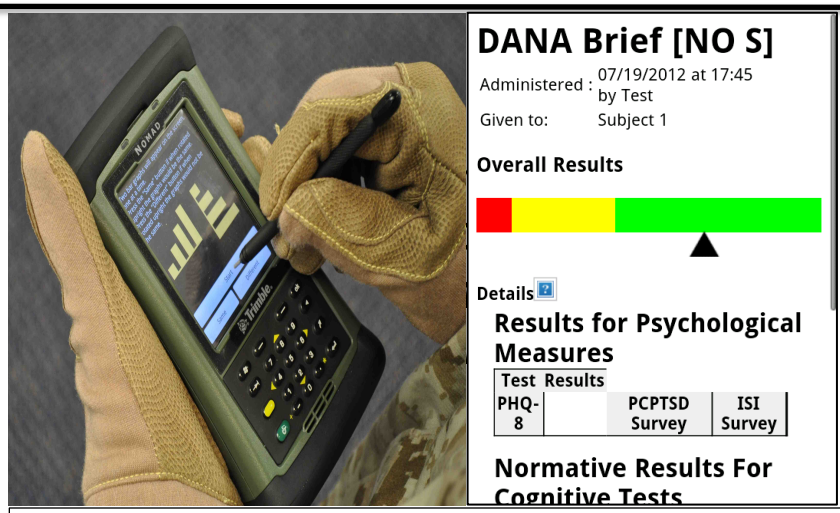
PI: Dr. Corinna Lathan **Org:** AnthroTronix, Inc. **Award Amount:** $3M

Study/Product Aim(s)

- Scientifically and clinically validate DANA
- Obtain FDA clearance for DANA
- Transition DANA to DoD

Approach

Three studies were conducted to validate DANA's efficacy in assessing change in cognitive function as a result of concussion, depression and PTSD. A 513(g) determination from the FDA will decide whether a 510(k) submission is necessary, and DANA will be transitioned to the DoD. We submitted a 510(k) and DANA received FDA clearance on October 15, 2014.



Accomplishment: All three studies have been completed, preliminary data analysis has been done, full data analysis is on-going and manuscript preparation is in-progress.

Timeline and Cost

Activities CY	13	14
IRB approval for scientific studies		
Conduct scientific studies		
Obtain FDA clearance		
Transition DANA		
Estimated Budget ($K)	**$1,800,000**	**$1,200,000**

Updated: (September 9, 2015)

Goals/Milestones (Example)

CY13 Goal – Obtain FDA clearance, and IRB approval for three studies.

✓ Submitted 513(g) RFI
✓ Submitted 510(k)
✓ Obtained IRB approval for all three studies.

CY14 Goal – Conduct scientific studies, publish results, transition DANA

✓ All studies completed data collection.
✓ Numerous manuscripts have been published showing that DANA is a reliable, consistent assessment tool.

Comments/Challenges/Issues/Concerns

- Delay in data analysis will require additional publications to be completed this coming year.

Budget Expenditure to Date

Projected Expenditure: $3,000,000
Actual Expenditure: $3,000,000

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center – WO66-G609
Silver Spring, MD 20993-0002

October 15, 2014

AnthroTronix, Inc.
Dr. Corinna Lathan
Chief Executive Officer
8737 Colesville Road, Suite L-203
Silver Spring, MD 20910

Re: K141865
Trade/Device Name: DANA
Regulation Number: Unclassified
Device Classification Name: Recorder, Attention Task Performance
Regulatory Class: Unclassified
Product Code: LQD
Dated: July 9, 2014
Received: July 10, 2014

Dear Dr. Lathan:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21

CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Felipe Aguel -S

for Carlos L. Peña, PhD, MS
Director
Division of Neurological
and Physical Medicine Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure